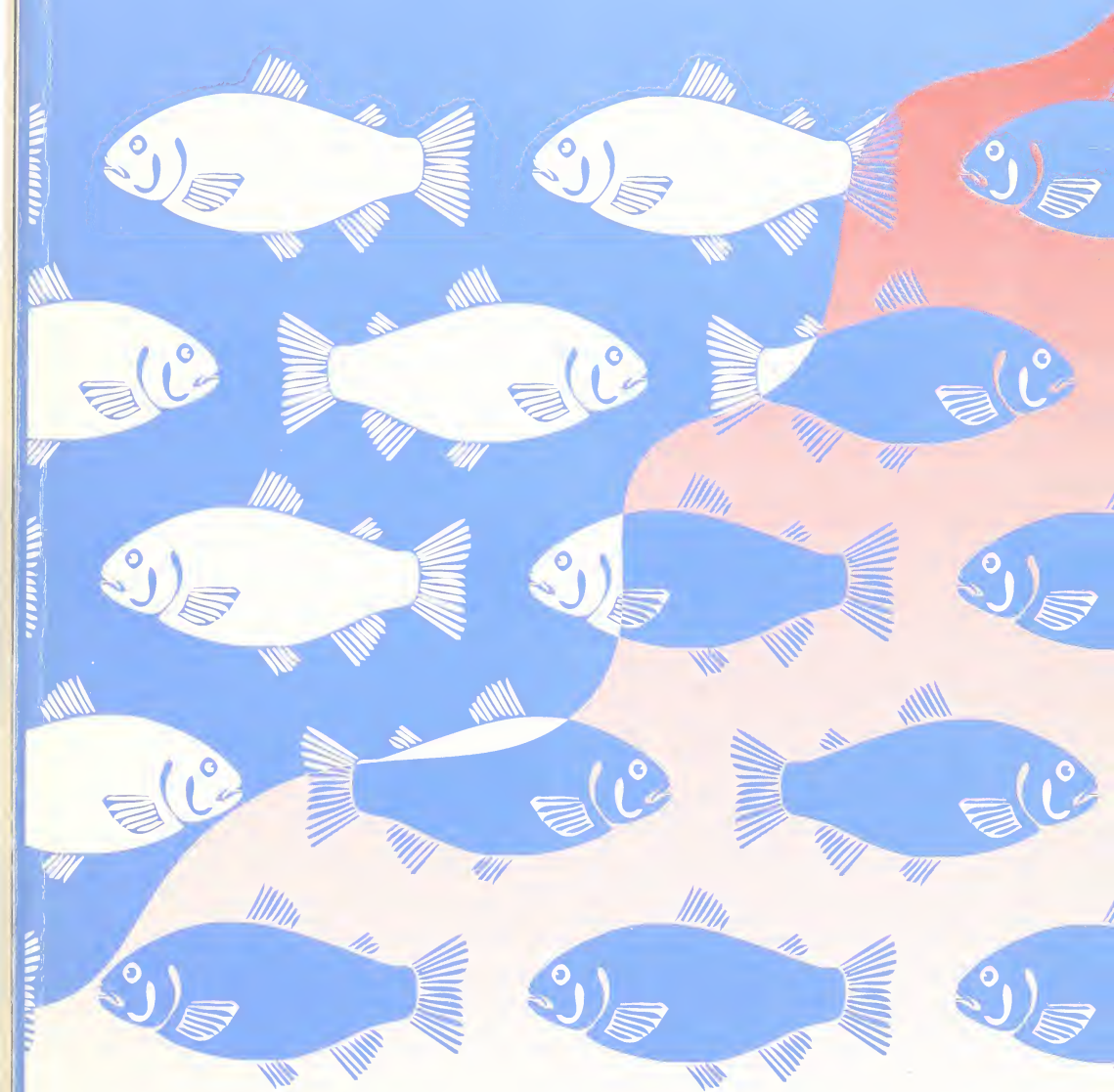
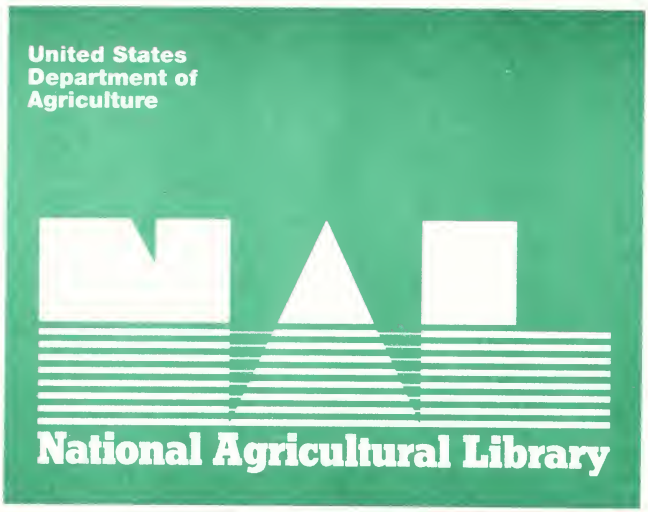
Federal Regulation of Drugs, Biologicals, and Chemicals Used in Aquaculture Production

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Federal Regulation of Drugs, Biologicals, and Chemicals Used in Aquaculture Production

Joint Subcommittee on Aquaculture,
Working Group on Quality Assurance in Aquaculture Production

Compiled by:

Food and Drug Administration,
U.S. Department of Health and Human Services,

U.S. Environmental Protection Agency, and

Animal and Plant Health Inspection Service,
U.S. Department of Agriculture

Coordinated through:

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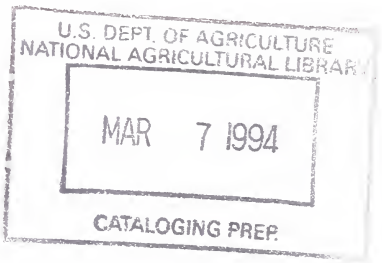

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PREFACE

Federal Regulation of Drugs, Biologicals, and Chemicals Used in Aquaculture Production was prepared by the Joint Subcommittee on Aquaculture's (JSA) Working Group on Quality Assurance in Aquaculture Production as a guide to Federal requirements associated with marketing and using these compounds. It provides a summary of Food and Drug Administration, Environmental Protection Agency, and Animal and Plant Health Inspection Service regulations applicable to these compounds, as well as sources of contact for further information.

This booklet is intended as a general reference for aquaculture industry leaders, educators, and others who are engaged in providing information on the use of animal drugs, feeds, vaccines, herbicides, algicides, and related compounds in aquaculture situations.

The National Aquaculture Improvement Act of 1985 states that it is national policy to promote aquaculture in the United States by ... encouraging aquaculture activities and programs in both the public and private sectors of the economy. It recognizes that aquaculture in the United States is a viable approach toward meeting food needs. It also recognizes that aquaculture provides resources for industrial materials, pharmaceuticals, and energy, and

assists in pollution control. As a whole, the aquaculture industry can help reduce the U.S. trade deficit and alleviate the world's hunger and natural resource problems.

The JSA is a statutory committee that operates under the aegis of the Federal Coordinating Council on Science, Engineering, and Technology, in the Office of the Science Advisor to the President. The mission of the JSA is to serve as a coordinating group to increase the overall effectiveness of Federal programs in aquaculture. The Secretary of Agriculture was designated as the permanent chairman, with USDA serving as the lead Federal agency for the coordination and dissemination of aquaculture information. At present, 23 Federal departments and their agencies are represented in the JSA. The JSA is composed of the following members or their designees:

Secretary of Agriculture
Secretary of Commerce
Secretary of the Interior
Secretary of Energy
Secretary of Health and Human Services
Administrator of the Environmental Protection Agency
Chief of Army Corps of Engineers
Administrator of the Small Business Administration
Administrator of he Agency for International Development
Chairman of the Tennessee Valley Authority
Director of the National Science Foundation
Governor of the Farm Credit Administration
Heads of such other Federal agencies as are deemed appropriate by the Director of the Office of Science and Technology Policy.

The Working Group on Quality Assurance in Aquaculture Production was established as a JSA Task Force in November 1990, to coordinate industry efforts to increase understanding of Federal requirements regarding drug, biological, and chemical use in aquaculture production. It is composed of representatives from:

Federal and State Agencies

Food and Drug Administration
Extension Service-USDA
Environmental Protection Agency
U.S. Fish and Wildlife Service
National Agricultural Library-USDA
Food Safety and Inspection Service-USDA
Cooperative State Research Service-USDA
State Departments of Wildlife

Commercial, Educational, and Private Organizations

American Fisheries Society
American Tilapia Association
Atlantic Coast Shellfish Producers Association
Baitfish Industry
Catfish Farmers of America
Center for Tropical and Subtropical Aquaculture
Florida Tropical Fish Farms Association
Louisiana Crawfish Farmers Association
Maine Aquaculture Association
National Aquaculture Association
National Aquaculture Council of the
National Fisheries Institute
National Association of State Aquaculture Coordinators
National Ornamental Goldfish Growers Association, Inc.
Pacific Coast Oyster Growers Association

Striped Bass Growers Association
United States Trout Farmers Association
University of Arizona
Washington Fish Growers Association

ACKNOWLEDGMENTS

Development of this guide to ***Federal Regulation of Drugs, Biologicals, and Chemicals Used in Aquaculture Production*** was supported by the United States Department of Agriculture's Cooperative State Research Service (CSRS) Office of Aquaculture, the Food and Drug Administration's Center for Veterinary Medicine (CVM), and the Catfish Farmers of America (CFA). The Working Group members acknowledge the collaborative efforts and funding provided by CSRS, CVM, and CFA.

A special appreciation is expressed to Drs. R. Oneal Smitherman and Henry S. Parker for their encouragement and commitment to this JSA project.

We also acknowledge Mr. Antonio Bravo, Environmental Protection Agency, Dr. Althaea Langston, Animal and Plant Health Inspection Service, USDA, and Ms. Joanne Kla, CVM, Food and Drug Administration, for their assistance in assembling this information and obtaining approval clearances. Ms. Eileen McVey, AIC, NAL, is acknowledged for her assistance with desktop publishing and final editing.

Gary E. Stefan
Chair, Working Group on Quality Assurance in Aquaculture Production

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PART I

FOOD AND DRUG ADMINISTRATION

Section 1. Legal Authority

The mission of the Food and Drug Administration is to enforce laws enacted by the U.S. Congress and regulations promulgated by the Agency to protect the consumer's health and safety, and to protect the consumer from economic fraud.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301-392) is the basic food and drug law of the United States. With numerous amendments it is the most extensive law of its kind in the world. Many of the states in the United States have laws similar to the Federal law, and some have provisions to add automatically any new Federal requirements.

The law is intended to assure the consumer that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs (including animal drugs) and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Section 512 of the Act, the basic statutory provision governing new animal drugs, provides that a new animal drug shall be deemed unsafe unless there is in effect an approval of a new animal drug application and that the

intended use of a drug and its labeling must conform to the approved application. A drug which does not conform to the provisions of section 512 is deemed adulterated and is subject to the enforcement provisions of the Act. The Act provides an exception for investigational use of an unapproved new animal drug under conditions prescribed by FDA regulations.

Virtually all animal drugs are new animal drugs within the meaning of the term in the Act, and so are subject to section 512. Although an animal drug may avoid the approval requirement if it is not a new animal drug or is grandfathered, the burden is on the marketer to prove that one of these exceptions applies. To assist in carrying out its statutory responsibilities, the FDA has promulgated regulations and developed written regulatory policies. New regulations are published in the Federal Register. All FDA regulations are codified in Title 21 of the Code of Federal Regulations. These regulations and policies are subject to change as new circumstances occur and new information becomes available. Because they are always subject to legal challenge, they must be scientifically and legally defensible.

The Federal Food, Drug, and Cosmetic Act prohibits distribution in the United States of articles that are adulterated or misbranded. The term adulterated includes products that are defective, unsafe, filthy, produced under insanitary conditions or, for drugs and feed additives, not approved by FDA (Secs. 402, 501, 601). Misbranded includes statements, designs, or pictures in labeling that are false or misleading, and failure to provide required information in labeling (Secs. 403, 502, 602). Detailed definitions of adulteration and misbranding are in the law itself, and hundreds of court decisions have interpreted them.

Section 2. Animal Drugs

A. The Drug Approval Process

Under the Federal Food, Drug, and Cosmetic Act, the term drugs means articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary; articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles other than food intended to affect the structure or any function of the body of man or other animals. It also includes articles intended for use as a component of a drug.

Once a product is determined to be a drug for animal use, the next step is to determine whether or not it is a new animal drug. The Act defines a new animal drug (in part) as any drug intended for use for animals other than man, the composition of which is not generally recognized, among experts qualified by scientific training and experience, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling. By virtue of Supreme Court interpretations of the necessary basis for general recognition, there are, for all practical purposes, no animal drugs which are not also new animal drugs.

Before a new animal drug may receive formal FDA approval, it must be established by scientific testing as effective and safe by the sponsor of the drug product.

Effective means that the product will do what it is claimed it will do consistently and uniformly. Safe includes safety to the animal, safety of food products derived from the animal, safety to persons administering the drug or otherwise associated with the animal, and safety in terms of the drug's impact on the environment.

If the product is intended for use in a food-producing animal, residues in food products must also be established as safe for human consumption. The sponsor must also develop analytical methods to detect and measure drug residues in edible animal products. It is the responsibility of the drug sponsor (individual or firm seeking FDA approval of the drug product) to conduct the necessary tests.

The sponsor may select outside investigators to conduct clinical trials of the drug as long as they are qualified by scientific training and experience, and agree to comply with the investigational protocol and all applicable regulations. FDA has established regulations for non-clinical investigations, such as toxicology studies, and regulations and guidelines for conducting and monitoring clinical trials.

When the sponsors believe that sufficient data have been collected to establish the safety and effectiveness of their drug product, they may apply for approval. A New Animal Drug Application (NADA) is submitted along with supporting data, including all adverse effects associated with the drug's use. The NADA must also include information on the drug's chemistry; composition and component ingredients; manufacturing methods, facilities, and controls; proposed labeling; analytical methods for residue detection and analysis if applicable; an environmental impact assessment; and other information.

The FDA review of the NADA submitted by drug sponsors is very detailed and comprehensive. FDA scientists will determine whether the data have been developed in

accordance with Good Laboratory Practice Regulations and the clinical trial guidelines. If the studies were conducted properly, the data are evaluated with respect to drug safety and effectiveness. The animal safety data for a drug product must relate to the dosage levels and routes of administration proposed in the labeling. The primary objective is to determine the safety of the product relative to labeled usage. Examples of some questions that must be answered concerning the safety of the drug product to the animal are:

1) What is the toxicity in the target animal?

2) Is the product a teratogen, carcinogen, or mutagen?

3) What is the margin of safety?

4) Are observed toxic effects (if any) reversible?

5) Does the product affect reproduction?

At the conclusion of the animal safety review, a summary is prepared which explains why the product is safe or not shown to be safe. If the product has been shown to be safe but some restrictions or constraints on use are needed, all warning and caution statements to be placed on the label must be enumerated and included in the summary, as well as any expected side effects.

All effectiveness data submitted must relate either directly or indirectly to the specific label and labeling claims made for the product. Basically, the petitioner must demonstrate that the product produces the claimed effect. As a minimum, the data must have four basic attributes:

1) The data must come from adequate and well-controlled studies.

2) The data must demonstrate that the dose response relationship has been established.

3) The studies must have been performed in several locations so that any geographic or environmental effects can be evaluated.

4) The major portion of the data must come from studies in which the proposed label dosages and routes of administration were used.

Since no drug is absolutely safe or totally effective, approval of a drug product from a target species standpoint must rest on an assessment of the degree of acceptable risk when weighed against the potential therapeutic benefit. Such risk/benefit weighing is not done with respect to human food safety.

With respect to human food safety, the Center for Veterinary Medicine makes a threshold assessment of the carcinogenic potential of the drug. In some cases, sponsors are required to submit results of extensive testing to determine the cancer-causing potential. Food animal drugs that are cancer producing, or whose metabolites are cancer producing, may be approved only if no harm comes to the animal and there is no residue of the substance or its metabolites in edible tissues reaching the consumer. Extensive testing may be required to establish the no-residue level based on a risk calculation. In general, sponsors of food animal drugs are required to submit toxicity and metabolism studies, as well as residue depletion studies upon which FDA can base a withdrawal time for the drug.

Development of adequate methods for detecting drug residues and their metabolites is frequently a very time-consuming and expensive item in developing a new animal drug for food-producing animals. Analytical methods sensitive to levels that assure food safety may have to be developed for muscle or other tissues. The proposed residue methodology must be validated prior to approval of the NADA and must show satisfactory performance in one USDA and two FDA laboratories. If

the method proves to be practical, of sufficient sensitivity, and is validated in the three laboratories, FDA will approve the method.

When an NADA is approved, a regulation is published in the Federal Register announcing its approval and is incorporated into the Code of Federal Regulations.

Under certain conditions, unapproved new animal drugs may be distributed and used under the terms of Investigational New Animal Drug (INAD) applications. The drugs must be used for research, i.e., for the collection of data that must be submitted in support of an NADA approval. Regulations provide that such drugs may be distributed for use by experts, qualified by scientific training and expertise, to investigate the safety and effectiveness of animal drugs.

B. Classifying Rx and OTC Animal Drugs

FDA has the responsibility for determining the marketing status (prescription or over-the-counter) of animal drug products based on whether or not it is possible to prepare adequate directions for use under which a layperson can use the drugs safely and effectively. An animal drug which, because of its toxicity or other potentiality for harmful effects, or method of its use, or the collateral measures necessary for its use, is not safe for animal use except under the professional supervision of a licensed veterinarian is an Rx drug and can be dispensed only by or upon the lawful written order of a licensed veterinarian. Products for which adequate directions for lay use can be written must be labeled for over-the-counter (OTC) use under existing law. If adequate directions cannot be written, the prescription (Rx) system provides a method of distribution and control which is intended to assure that the Rx product reaches only the hands of persons trained to use the product. This can include, in addition to the

veterinarian, animal owners or managers who the veterinarian has determined are capable of using the product safely under the practitioner's supervision.

Effective use of a drug product assumes that an accurate diagnosis can be made with a reasonable degree of certainty, that the drug can be properly administered, and that the course of the disease can be followed so that the success or lack of success of the product can be observed.

The same drug substances can be marketed in a number of different dosage forms, intended for use by different routes of administration, and in different species of animals. Thus, these drug products may be appropriately labeled Rx in some cases and OTC in others.

Rx products must bear the legend:

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

C. Extra-label Use of New Animal Drugs in Food-producing Animals

Extra-label use refers to the actual or intended use of a new animal drug in a food-producing animal in a manner that is not in accordance with the approved drug labeling. If an approved new animal drug is used for an unlabeled purpose, it is deemed unsafe under section 512 (a)(1)(B) and is in violation of the law. Extra-label use includes, but is not limited to, use in species or for indications not listed in the labeling, or use at dosage levels other than those stated in the labeling.

The law does not provide a special exemption that allows veterinarians to make extra-label uses of drugs. However, the Agency recognizes that there are some species and disease conditions for which no drugs are approved, and

that animals might suffer or die if they are not treated in an extra-label manner. Therefore, the Agency has adopted an extra-label drug use policy which describes circumstances under which a veterinarian might consider extra-label uses. The policy is stated in FDA Compliance Policy Guide 7125.06, Extra-label Use of New Animal Drugs in Food-producing Animals, and is available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

D. Dispensing Veterinary Prescription Drugs

Since adequate directions for safe and effective lay use cannot be written for veterinary prescription drug products, such products can only be sold to or on the prescription or other order of a licensed veterinarian (section 503 (f)). Prior to being sold or dispensed, they must remain in the possession of a person or firm regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale or retail distribution of veterinary prescription drug products. The drug products may be distributed only by persons or firms authorized by state and local laws.

Sale (dispensing, shipping, or otherwise making available for use in animals) to the layperson of a veterinary prescription drug product may be made only by or on the bona fide prescription or other order of a licensed veterinarian. The FDA has interpreted the word prescription to apply only to the practitioner's direction to a pharmacist. Because some states authorize persons other than pharmacists to dispense prescription drug products on a veterinarian's instructions, the term other order is used when instructions are for a legally authorized dispenser who is not a pharmacist. In both cases the instructions and their intent are the same and the dispenser may not dispense an Rx drug product without a veterinarian's explicit authorization.

Sale of a veterinary prescription legend drug product to a layperson, except on a prescription or on order of a licensed practitioner, causes the product to be misbranded and subjects the seller to civil and/or criminal provisions of the Act.

A licensed veterinarian may legally use or dispense a veterinary prescription drug product only within the course of his/her professional practice where a valid veterinarian-client-patient relationship exists. Veterinarians employed by drug manufacturers or distributors may not legally dispense prescription drug products to laypersons unless they meet the above criteria. Similarly, practicing veterinarians or their employees may not legally sell veterinary prescription drug products to walk-in customers unless the same criteria are met.

Federal regulations require that drug manufacturers provide at least the following information on the label of the finished package form of veterinary prescription drug products:

1) the statement: **Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian;**

2) recommended or usual dosage;

3) the route of administration, if it is not for oral use;

4) the quantity or proportion of each active ingredient;

5) the names of inactive ingredients if it is for other than oral use;

6) an identifying lot or control number;

7) manufacturer, packer, or distributor's name and address; and

8) net quantity contents.

When dispensed by a licensed veterinarian, the drug must bear a label containing the name and address of the practitioner and any directions for use and cautionary statements specified by the practitioner.

When issuing a prescription or other order, the veterinarian must inform the pharmacist or authorized dispenser as to the information to be placed on the labeling of the dispensed product which must include at a minimum the information listed below:

1) name and address of the dispenser;

2) serial number and date of the order or its filling;

3) name and address of the veterinarian who prescribed or ordered the drug product;

4) directions for use; and

5) any necessary cautionary statements including withdrawal times.

E. Bulk New Animal Drug Substances

Bulk new animal drugs (sometimes called bulk drugs or chemicals) are new animal drug substances intended for use in the preparation of a finished dosage form new animal drug product. The importation or domestic distribution of bulk new animal drugs by producers (or anyone else) for treating animals is illegal unless the drugs are intended for use in the manufacture of finished drug products that are the subject of approved NADAs, or the manufacture of drug products intended for investigational use in accordance with FDA regulations.

F. Minor Use Drugs

Minor use means the use of new animal drugs in animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats, or the use of new animal drugs in any species for the control of a disease that occurs infrequently or in limited geographic areas. FDA regulations (21 CFR 514.1) allow sponsors, where appropriate, to use data supporting an approved major use of a drug to support an NADA for a minor use of the same drug. This minor use regulation does not negate or alter the legal requirements to show safety and to demonstrate effectiveness. The regulation does, however, provide for the Agency's interpretation as to what data for minor use drugs will be sufficient to meet the legal standards.

Guidelines for the preparation and submission of data to satisfy the requirements of section 512 of the Act regarding animal safety, effectiveness, human food safety, and environmental considerations for new animal drugs intended for a ***minor use*** are available from the Communications and Education Branch (HFV-12). Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

Animal Safety and Effectiveness. Where the guidelines do not specifically provide for a particular minor use, the Center for Veterinary Medicine, upon request, will advise interested persons on the effectiveness and animal safety data regarding the minor use that will be needed to satisfy the requirements of section 512 of the Act. Where scientifically appropriate, the Center for Veterinary Medicine will allow the extrapolation of data from a major species to a minor species to satisfy the requirements of the Act.

Human Food Safety and Environmental Guidelines. The human food safety and environmental guidelines do not specifically provide for a particular ***minor use***. Therefore,

the Center for Veterinary Medicine will, upon request, advise interested persons of the data that will be needed. Where scientifically appropriate, the Center for Veterinary Medicine will allow the extrapolation of data from a major species to a minor species to satisfy the requirements of the Act.

Sponsors of minor use drugs may have access to data supporting the safety and effectiveness of the approved major use drug only if the holder of the approval agrees or if the data are publicly available.

G. Reporting Adverse Drug Reactions

Users of new animal drug products are encouraged to notify the product's sponsor of any unexpected or adverse reactions resulting from the use of that product. The sponsor is responsible for establishing and maintaining records concerning experiences with the drugs and for submitting reports of those experiences to FDA. Among the data which must be submitted are reports of injury, toxicity, sensitivity reaction, unexpected incidence or severity of side-effects associated with use, or failure of the drug to exhibit expected pharmacological action. FDA scientists analyze this data to determine if any modifications are needed in the drug's labeling, dosage level, etc., to prevent future adverse reactions. In extreme instances, the adverse reactions may be so severe as to require withdrawal of approval of the drug. However, because of the extensive premarketing approval process, this rarely occurs.

FDA also encourages direct reporting of adverse drug reactions by veterinarians. The reports should be submitted on Form FDA 1932a, Veterinary Alert to Adverse Reaction. This is a pre-addressed, postage-paid form which is filled out and dropped in the mail by the veterinarian. Copies of the form are usually available from state veterinary medical associations, clinics of colleges of

veterinary medicine, USDA Extension Service veterinarians, and FDA offices. FDA may occasionally need more detailed information about an incident, and the veterinarian may be called by an FDA staff veterinarian. In any event, all forms are acknowledged by letter and another form is sent for future use.

Adverse reactions may be reported by telephone during normal working hours (7:00 a.m. to 4:00 p.m. Eastern Standard/Daylight Time) by calling collect 301-295-8751, or after hours by dialing direct 301-295-8797. In the second case a message is recorded and the call is returned by a veterinarian the following working day.

H. Registration and Drug Listing

The Federal Food, Drug, and Cosmetic Act [section 510(a)] requires that the owner or operator of an establishment, not exempt under section 510(g), that engages in the manufacture, preparation, propagation, compounding, processing, repackaging, or relabeling of drugs, must register annually with the Food and Drug Administration.

Owners who use Type A medicated articles (drug premixes) to prepare feed for their own animals are exempt from registration unless they manufacture feeds that are required to be the subject of an approved NADA or a medicated feed application.

Registration is required annually. Establishments currently registered will be sent a necessary form to register (FDA-2656) for the following year. Establishments not previously registered will use Form FDA-2656 Registration of Drug Establishment. These forms and instructions are available from any of the FDA field offices or from the FDA Drug Registration Staff, National Center for Drug Evaluation and Research, 7500 Standish Place, Rockville, MD 20855. Owners or

operators of establishments not previously required to register must register within five (5) days after the startup of manufacturing or processing operations. However, those operators who are submitting NADAs or Medicated Feed Applications must register prior to engaging in the manufacture or processing of the medicated premixes, concentrates, supplements, or finished feeds as a prerequisite for approval of the applications.

The Drug Listing Act of 1972 amending the FFDCA [section 510 (J) (1)] requires that all firms (establishments) that must register must also list the drugs which they market whether used in interstate commerce or not. Form FDA-2657, Drug Product Listing, is used for drug product listing.

All animal drugs and medicated animal feeds are subject to the Drug Listing Act. However, only animal dosage form drugs and type A medicated articles for feed manufacture must be listed. Medicated feeds do not have to be listed.

Owners of establishments that manufacture or process drugs subject to drug listing must update their drug listing information annually. Section 207 of the FDA regulations, 21 CFR, provides more details.

PART I: FOOD AND DRUG ADMINISTRATION

Section 3. Animal Feeds

A. Food Additive Petition Process

With certain exceptions, substances which, by their intended uses, may become components of animal feeds either directly or indirectly, or which may otherwise affect

the characteristics of animal feed, are food additives. The definition of food additives includes substances intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding feed that might become components or otherwise affect the characteristics of animal feed. It also includes any source of radiation for such use. The exceptions include substances which are Generally Recognized As Safe (GRAS) for particular uses; which are the subject of certain prior sanctions; and which are new animal drugs, color additives, or pesticides.

Food additives are illegal unless they are the subject of a published regulation providing for their safe use. Food additives which are cancer producing, or whose metabolites are cancer producing, may be used in feed for food-producing animals only if no harm comes to the animal and there is no residue of the substance or its metabolites in edible tissues reaching the consumer. Food additive regulations are based on data submitted in the form of a food additive petition. Food additive petitions pertaining to animal feed should be submitted to the Center for Veterinary Medicine, Division of Animal Feeds, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

The kinds of data which must be submitted in a food additive petition (FAP) are similar to those required in an NADA. The following areas must be addressed in an FAP: chemical identity, amount proposed for use, intended physical or other technical effect, feed assay, animal and human safety, tolerances, proposed regulation, and environmental assessment.

Food additive petitions are administered differently from NADAs because the statutory requirements are different. The Code of Federal Regulations [21 CFR 571.1(i)(1)] requires that the sponsor of a food additive petition be notified within 15 days following receipt that the petition is either acceptable or not acceptable for filing. Section

571.1(i)(2) requires that within 30 days after the petition is filed, a notice of the filing shall be published in the ***Federal Register.***

Section 409(c)(2) of the FFDCA requires the issuance of a final order within 90 days after the date of filing of the petition, or the petitioner must be notified in writing that the 90-day period is being extended to 180 days. 21 CFR 571.6 states that if the petitioner amends the FAP with data which are determined to be a substantive amendment, the petition, as amended, will be given a new filing date, and the time limitation will begin to run anew.

Any person has 30 days after publication of a final order (whether the order establishes a food additive regulation or denies the petition) to file objections thereto with the Secretary of the Department of Health and Human Services and to request a public hearing upon such objections. All final orders provide for a 30-day comment period in which to voice such objections.

A listing of food additives permitted in the feed and drinking water of animals is provided in 21 CFR 573. A listing of compounds generally recognized as safe (GRAS) is provided in 21 CFR 582.

B. Drugs in Animal Feeds (Medicated Feeds)

Anyone who adds drugs to feed is subject to the Federal Food, Drug, and Cosmetic Act. Just as each label claim for a new animal drug must be approved, so too must the drug be specifically approved for administration in animal feed. When the NADA for use of the compound in animal feed is approved, a regulation is published in the Federal Register. The approval is for a Type A medicated article. Type A medicated articles are concentrated premixes, contain one or more new animal drugs intended for use in the manufacture of a medicated feed, and are available only from a drug manufacturer or premixer. Type B

products are animal feeds containing a new animal drug intended solely to manufacture another Type B or Type C medicated feed. Type C products are also regulated as medicated feeds, but are more dilute. They are diluted to the approved feeding levels and may be offered as a complete feed, may be fed-top dressed, or may be offered free-choice. They are produced by substantially diluting a drug component, Type A medicated article, a Type B medicated feed, or another Type C medicated feed.

Those who wish to manufacture medicated feeds using the drug must follow the regulations, and may be required to submit a medicated feed application (MFA) for FDA approval. The purpose of the MFA is to show the Agency that the user of the Type A medicated article can adequately manufacture and properly label the medicated feed. Although the MFA is not very extensive, requiring considerably less information than an NADA, it places a legal obligation on the medicated feed manufacturer. The main components of an MFA are identification of the regulation that provides the basis for approval, documentation of a working understanding of the regulation, and a copy of the label for the medicated feed(s) covered by the application.

FDA's regulations classify all animal feed drugs into two categories. Category I drugs are those for which no withdrawal period is required at the lowest use level for each species for which they are approved. Category II drugs, on the other hand, are those for which a withdrawal period prior to slaughter of treated animals is required at the lowest use level for at least one species for which they are approved. A firm must obtain an approved MFA (FDA Form 1900) to use Type A Category II medicated articles to make Type B or C medicated feed.

The medicated feed regulations are based first and foremost on protection of human health by categorizing feed use drugs on the basis of residue potential. They provide uniformity and measure potential risk

consistently. The program also gives both commercial and on-farm feed mills a choice as to the degree of regulation they want, based on the drug products they choose. Both feed manufacturers and producers can use the higher potency drugs in mixing their feed and therefore be subject to medicated feed applications. Or they can choose the exempted route, using only Category I drugs and the Type B level of Category II drugs to make other Type B or C medicated feeds.

Information on the categorization of specific compounds and the procedures for obtaining a medicated feed application is available from:

Communications and Education Branch
(HFV-12)
Food and Drug Administration
Center for Veterinary Medicine
7500 Standish Place
Rockville, MD 20855

The medicated feed regulations are in 21 CFR 558.

C. Good Manufacturing Practice Requirements for Feed Mills

A most important responsibility of an animal feed manufacturer is to assure that the feed produced, whether medicated or non-medicated, meets the intended specifications and is not adulterated. All feed mixing operations, regardless of size or drugs used, share this responsibility. Medicated feeds must contain the proper amount of drug to have their intended effect. Medicated and non-medicated feeds that are adulterated with undesired drugs may cause violative drug residues in meat, milk, or eggs, or injury to consuming animals. Everyone associated with food animal agriculture must work to avoid

these risks to the public and animal health, and the potential loss of consumer confidence in animal-derived food products.

The Food and Drug Administration (FDA) established the Current Good Manufacturing Practice (CGMP) Regulations for Medicated Feeds (21 CFR 225) through public rulemaking. The CGMPs provide guidance for medicated feed manufacturers to assure that their products meet the identity, strength, and quality which they should possess with respect to their drug content. The regulations apply to **all** manufacturers of medicated feeds, commercial and on-farm, using the same drug sources. The regulations are divided into two sections. The first section applies to facilities utilizing drug sources which require registration with FDA. This section is more comprehensive and detailed than the second section. The second section applies to facilities which are not required to be registered. Medicated feeds must be manufactured in accordance with the appropriate applicable section of the CGMP regulations to comply with the law.

Registered feed mills are subject to biennial inspection. There is no routine FDA biennial inspection of those feed manufacturers not required to be registered. The fact that a feed manufacturing operation is not registered, however, does not mean that it is totally exempt from Federal inspection. An FDA investigator or an FDA-commissioned state inspector, may conduct an inspection to confirm registration status of the firm or to follow up on a report of a drug residue, or for other appropriate reasons. Also, the state feed control office may conduct routine inspections to determine compliance of the facility with the less detailed CGMP regulations.

By knowing the CGMP regulations and by self-inspection, establishment owners can determine if their operation complies with the spirit and intent of the regulations. Non-compliance may result in product adulteration and unacceptable risks to animal and/or public health. Mill

operators need to ensure that all employees involved in the manufacture of medicated feeds have an understanding of the manufacturing and control operation(s) which they perform, including the location and proper use of equipment, and that all necessary procedures and controls are in place and followed.

Part I: Food and Drug Administration

Section 4. Color Additives

The Federal Food, Drug, and Cosmetic Act provides that foods, drugs, cosmetics, and some medical devices are adulterated if they contain color additives that have not been proven safe to the satisfaction of the Food and Drug Administration for the particular use. A color additive is a dye, pigment, or other substance, whether synthetic or derived from a vegetable, animal, mineral, or other source, which imparts a color when added or applied to a food, drug, cosmetic, or the human body (section 201(t)).

Regulations (21 CFR 73, 74, and 81) list the approved color additives and the conditions under which they may be safely used, including the amounts that may be used when limitations are necessary. Separate lists are provided for color additives for use in or on foods, drugs, medical devices, and cosmetics. Some colors may appear on more than one list. Testing and certification by the Food and Drug Administration of each batch of color is required before that batch can be used, unless the color additive is specifically exempted by regulation.

Feed manufacturers, producers, processors, etc., who want to use color additives in animal feed should check the regulations to ascertain which colors have been listed for various uses.

For copies of regulations governing the listing, certification, and use of colors in foods, drugs, devices, and cosmetics shipped in interstate commerce or offered for entry into the United States, or answers to questions concerning them, contact:

Division of Color Technology, HFF-434
Food and Drug Administration
200 C Street, S.W.
Washington, DC 20204

PART I: FOOD AND DRUG ADMINISTRATION

Section 5. Enforcement

A. Responsibility for Illegal Residues in Meat, Fish, Milk, and Eggs

FDA is responsible for programs and regulatory actions aimed at preventing illegal drug residues in human food products derived from treated animals. Illegal drug residues in edible products can constitute a hazard to the health of persons consuming such food. Failure to observe label withdrawal periods before slaughter or processing, or failure to withhold milk is the principal cause of illegal drug residues. Other causes may include failure to follow other label directions, poor feed manufacturing practices, and human negligence. FDA is also charged with ensuring that contaminants of feed origin do not result in unsafe contamination in human food of animal origin. Regardless of the cause, it is FDA's policy to hold responsible any individual in the production and marketing chain who can be shown to have caused (by an act of commission or omission) illegal residues or other contaminants in edible animal products. If justified by the facts, legal charges will be considered against these individuals.

B. Types of FDA Regulatory Actions

The objective of FDA regulatory programs is to assure compliance with the Federal Food, Drug, and Cosmetic Act. Specific enforcement activities include actions to correct and prevent violations, remove violative products or goods from the market, and punish offenders. The types of enforcement vary with the nature of the violation. They range from a letter notifying the individual or firm of a violation and requesting correction, to criminal prosecution of the individual or firm. Findings of adulteration or misbranding usually lead to an individual who failed to take steps to assure compliance with the law. Such individuals can be charged as violators and, if guilty, are subject to the penalties specified by the law.

Warning letters are sent to the individuals, advising them of specific noted violations. These letters require a written response as to the steps which will be taken to correct the violation. These letters constitute one form of non-compliance warning that can be issued under current agency policy.

Criminal prosecution may be recommended in appropriate cases for violation of any provision of any provision of the Food, Drug, and Cosmetic Act. Misdemeanor convictions, which do not require proof of intent to violate the Act, can result in fines and/or imprisonment up to one year. Felony convictions, which apply in the case of a second violation or intent to defraud or mislead, can result in fines and/or imprisonment up to 3 years. Fines (misdemeanor or felony) can be as high as $500,000 or more.

Under current FDA policy, criminal prosecution is usually preceded by warning to the firm or individual(s) involved.

Seizure - An action brought under admiralty proceedings against an animal feed, drug, or device which is in violation of the Federal Food, Drug, and Cosmetic Act for being adulterated and/or misbranded. The purpose is to remove a specific lot of goods from the channels of commerce.

Injunction - A writ granted by a court whereby one is required to do or refrain from doing a specific act. In most instances FDA seeks injunctions against individuals and/or corporations to prevent them from violating or causing violations of the Federal Food, Drug, and Cosmetic Act.

The FDA field offices have primary responsibility for initiating and recommending regulatory action. The type of action recommended will depend upon the nature of the violation and the public health concern, agency policy, previous history of violations by the firm, and other factors. FDA headquarters offices generally approve enforcement actions. Approved recommendations for regulatory action are transmitted to the Justice Department.

C. Enforcement Discretion

Regulatory agencies such as the FDA have virtually unlimited discretion in deciding whether to enforce the law in a given situation. However, the FDA cannot give an affirmative, unqualified sanction to an illegal activity, such as the marketing of an unapproved drug. For example, the courts have ruled that the FDA could not give unqualified permission to use a drug for a specified period, to allow time for the manufacturer to obtain an approval. On the other hand, the courts have allowed the Agency to develop regulatory priorities and to reveal those priorities to the public.

Section 6. Interaction With FDA

A. Obtaining General Information

The Food and Drug Administration is most effective in carrying out its mission under a policy of openness and free communication. All parties are best served when there is clear understanding of the FDA's regulations and policies and how they are administered. By operating under this policy, FDA hopes to create confidence in, and support for, programs that are intended to promote and protect the health and well-being of all.

FDA encourages anyone to contact the Agency for assistance, to supply information, or to report a problem with a product. To help direct requests to the proper location for response, we offer the following guidance:

To obtain information on the drug approval process or INADs contact:

Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
(HFV-100)
7500 Standish Place
Rockville, MD 20855

To obtain information on approved drugs, regulations, policies, or to submit suggestions or comments, address your letter to:

Food and Drug Administration
Center for Veterinary Medicine
Office of Surveillance and Compliance
(HFV-200)
7500 Standish Place
Rockville, MD 20855

To request copies of a specific FDA document:

Food and Drug Administration
Freedom of Information Staff (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

To report an adverse drug reaction:

Call Collect: 301-295-8751 from 7:00 a.m. - 4:00 p.m. Eastern Standard (or Daylight) Time, Monday-Friday. After hours call 301-295-8797 (not a collect call) to leave a message and your call will be returned by a veterinarian the next working day.

To report a violation of the Federal Food, Drug, and Cosmetic Act contact your nearest FDA office or:

Division of Compliance (HFV-230)
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place
Rockville, Md 20855
Telephone: 301-295-8726

B. FDA Offices

LOCATION	JURISDICTION
BOSTON DISTRICT One Montvale Avenue 4th Floor Stoneham, MA 02180 617-279-2051	Connecticut Maine Massachusetts New Hampshire Rhode Island Vermont
NEW YORK DISTRICT 850 - 3rd Avenue Brooklyn, NY 11232 718-965-5301	New York City Downstate New York Long Island
BUFFALO DISTRICT 599 Delaware Avenue Buffalo, NY 14202 716-846-4478	Upstate New York
NEWARK DISTRICT 61 Main Street West Orange, NJ 07052 201-645-3023	New Jersey
SAN JUAN DISTRICT P.O. Box 5719 Puerta de Tierra Station San Juan, PR 00906-5719 809-729-6884	Puerto Rico
PHILADELPHIA DISTRICT 2nd & Chestnut Streets Room 900, U.S. Customhouse Philadelphia, PA 19106 215-597-4390	Delaware Pennsylvania

BALTIMORE DISTRICT 900 Madison Avenue Baltimore, MD 21201 301-962-4012	District of Columbia Maryland Virginia West Virginia
ATLANTA DISTRICT 60 Eighth Street, N.E. Atlanta, GA 30309 404-347-4344	Georgia North Carolina South Carolina
ORLANDO DISTRICT 7200 Lake Ellenor Drive Suite 120 Orlando, FL 32809 407-648-6995	Florida
NASHVILLE DISTRICT 297 Plus Park Boulevard Nashville, TN 37217 615-736-7222	Alabama Tennessee
CHICAGO DISTRICT 433 W. Van Buren Street Room 1222 PO Bldg. Chicago, IL 60607 312-353-7379	Illinois
CINCINNATI DISTRICT 1141 Central Parkway Cincinnati, OH 45202-1097 513-684-3501	Kentucky Ohio
DETROIT DISTRICT 1560 E. Jefferson Avenue Detroit, MI 48207 313-226-6260	Indiana Michigan

MINNEAPOLIS DISTRICT 240 Hennepin Avenue Minneapolis, MN 55401 612-334-4102	North Dakota Minnesota South Dakota Wisconsin
DALLAS DISTRICT 3032 Bryan Street Dallas, TX 75204 214-655-5315	Arkansas Oklahoma Texas
NEW ORLEANS DISTRICT 4298 Elysian Fields Avenue New Orleans, LA 70122 504-589-2401	Louisiana Mississippi
KANSAS CITY DISTRICT 1009 Cherry Street Kansas City, MO 64106 816-374-6371	Iowa Kansas Missouri Nebraska
DENVER DISTRICT P.O. Box 25087 Denver, CO 80225-0087 303-236-3017	Colorado New Mexico Utah Wyoming
SAN FRANCISCO 506, Federal Office Bldg. 50 U. N. Plaza San Francisco, CA 94102 415-556-0318	California (Northern) Hawaii Nevada
LOS ANGELES DISTRICT 1521 W. Pico Boulevard Los Angeles, CA 90015-2486 213-252-7586	Arizona California (Southern)

SEATTLE DISTRICT
22201 23rd Drive, S.E.
Bothell, WA 98021-4421
206-486-8788

Alaska
Idaho
Oregon
Washington
Montana

PART II

ENVIRONMENTAL PROTECTION AGENCY

Section 1. Legal Authority

The Environmental Protection Agency (EPA) regulates pesticides under two laws, the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The FFDCA gives EPA the authority to set legally enforceable limits, or tolerances, for pesticide residues in foods. The FFDCA specifies that a food containing a pesticide for which no tolerance has been established, or with a residue exceeding an established tolerance, is considered adulterated and subject to seizure. EPA sets tolerances for pesticide residues remaining in raw agricultural commodities under section 408 of the FFDCA. Under section 409 of the FFDCA, EPA sets food additive tolerances for pesticide residues which concentrate in processed foods above raw food tolerances, or which are the result of pesticide application during or after food processing.

Under FIFRA, all pesticides must be registered with EPA before they may be sold or distributed in commerce. FIFRA sets an overall risk/benefit standard for pesticide registration, requiring that pesticides perform their intended function, when used according to labeling directions, without posing unreasonable risks of adverse effects on human health or the environment. In making

pesticide registration decisions, EPA is required by law to take into account the economic, social, and environmental costs and benefits of pesticide uses.

FIFRA was first enacted in 1947. Thousands of pesticide products have been registered since then. However, the standards for pesticide registration have not remained the same since 1947, but have evolved in tandem with science and public policy. In particular, test data requirements for pesticides have become increasingly stringent in light of advances in such areas as toxicology and analytical chemistry. Under FIFRA, pesticide registrants (companies that hold pesticide registrations) are responsible for providing all test data necessary to satisfy EPA's registration requirements.

To ensure that previously registered pesticides measure up to current scientific and regulatory standards, FIFRA requires the review and reregistration of all existing pesticides.

FIFRA authorizes EPA to cancel the registration of an existing pesticide if test data show that it causes unreasonable adverse effects on human health or the environment. In addition, under certain circumstances, EPA may take action to suspend the registration of a pesticide to prevent an imminent hazard.

Section 2. Pesticides

A. Registration

General Information. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires that before any person in any state or foreign country can sell or distribute any pesticide in the United States, he or she must obtain a registration (or license) from the U.S. Environmental Protection Agency (EPA). FIFRA also provides that the Administrator may specify devices that are subject to the provisions of FIFRA.

The term ***pesticide*** means any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, and any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant.

The term ***pest***, as defined in FIFRA section 2(t), means (1) any insect, rodent, nematode, fungus, or weed, or (2) any other form of terrestrial or aquatic plant or animal life or virus, bacteria, or other microorganism (except viruses, bacteria, or other microorganisms on or in living humans or other living animals) which the Administrator declares to be a pest.

A ***device*** is any instrument or contrivance (other than a firearm) intended for trapping, destroying, repelling, or mitigating any pest or any other form of plant or animal life (other than man and other than a bacterium, virus, or other microorganism on or in living man or living animals) but not including equipment used for the application of pesticides (such as tamper-resistant bait boxes for rodenticides) when sold separately.

Pest Control Organisms, Substances, or Devices Not Subject To Registration Under FIFRA

40 CFR 152, Subpart B - Exemptions, describes those pesticides that have been exempted by the EPA from the registration requirements of FIFRA.

40 CFR 152.20 describes those pesticides, such as (1) certain biological control agents and (2) certain human drugs, that are exempted because they are regulated by another agency.

40 CFR 152.25 describes those pesticides, such as (1) treated articles or substances, (2) pheromones in pheromone traps, (3) preservatives for biological specimens, (4) vitamin-hormone horticultural products, and (5) foods, that are of a character not requiring regulation under FIFRA.

40 CFR 152.30 provides information on pesticides that may be transferred, sold, or distributed without registration.

Pest control organisms such as insect predators, nematodes, and macroscopic parasites are exempt from the requirements of FIFRA under 40 CFR 158.65(b)(3).

Devices considered not subject to registration include articles that use physical or mechanical means to trap, destroy, repel, or mitigate any plant or animal life declared to be a pest under 40 CFR 152.5. Other devices are subject to regulation under the provisions of FIFRA section 2(q)(1) or FIFRA section 7, even though they are not required to be registered.

Types of Pesticide Registration

There are two general types of pesticide registration available. You may (1) obtain a registration for your own product, or (2) become a supplemental registrant (often termed a distributor or subregistrant) for a product that someone else has already registered. These types of registrations, together with amendments to a registration, are described in more detail below.

Obtaining a Registration for Your Own Product

If you wish to obtain the registration for your own pesticide product, you are responsible for submitting all of the information and data that are required to support the registration. The information includes forms, proposed product labeling, technical and scientific data that are required on the specific product that you intend to make (or formulate), and information on how you will comply with the data compensation requirements. (See EPA's publication General Information on Applying for Pesticide Registration in the United States, June 1989, for detailed instructions on how to submit your registration.)

Obtaining a Supplemental Registration To Distribute a Product Registered by Someone Else

If you do not wish to take the time and expense necessary to register your own product, but would rather market a product that is currently registered to another company and you are willing to enter into an agreement with that company, the basic registrant may include you as a supplemental registrant to his or her registration so that you may market the product under your name.

Amending the Registration of a Product You Have Already Registered With the EPA

If you have a product that is already registered with the EPA, and wish to change the formulation or labeling text (i.e., add, delete, or change formulation components or label precautionary statements, add or change uses) you must file an application to amend the registration of your product. There are certain changes that you may make that require that you notify the EPA of the change, and other changes that require no notification at all.

Whom To Contact for Additional Information

If you have any questions, or require additional information concerning your application for registration, contact the Product Manager assigned the pesticide in your product.

If you have questions of a general nature that do not pertain to any specific pesticide, or that pertain to a new pesticide active ingredient for which you have not made an application, contact the Branch Chief for the type of pesticide (i.e., insecticide, fungicide, antimicrobial, etc.) about which you have a question.

If you have any questions concerning devices, whether they are subject to the Act, or establishment registration, please contact the Office of Compliance Monitoring, Compliance Division, (EN-342), Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Telephone: 202-260-7835.

Application for Registration of Pesticide-Producing Establishments

If you produce or formulate your own pesticide, then the place(s) [or establishment(s)] in which you produce a pesticide, or device, is subject to registration.

To submit application for pesticide-producing establishments:

1) Complete EPA Form 3540-8, Application for Registration of Pesticide-Producing Establishments.

2) Submit your application to one of the following offices:

Domestic Establishments - Submit your application to the EPA Regional Office having jurisdiction over the state in which the headquarters of your company is located.

Foreign Establishments - Foreign companies should submit their application to EPA's headquarters office at the address listed below:

Environmental Protection Agency
Office of Compliance Monitoring (EN-342)
401 M Street, S.W.
Washington, DC 20460 U.S.A.

40 CFR 167, entitled Registration of Pesticide Producing Establishments, Submission of Pesticide Reports, and Labeling, provides detailed information concerning definitions, registration procedures, labeling, and reporting requirements.

An ***establishment*** is defined as any site where a pesticide or device is produced, regardless of whether:

1) the site is independently owned or operated, or

2) the site is domestic (located in the U.S.) and is producing the pesticide or device only for export, or

3) the site is located in a foreign country and is producing the pesticide or device for importation into the United States.

The term *produce* is defined as the manufacture, preparation, propagation, compounding, or processing of any pesticide or device (including pesticides produced for use under an Experimental Use Permit), or the repackaging or the changing of the container of any pesticide or device.

Your application for the registration of your establishment requires the following information:

1) The name and address of your company,

2) The type of ownership (individual, partnership, cooperative association, corporation, or any organized group of persons whether incorporated or not), and

3) The names and addresses of all producing establishments.

Where To Obtain Application Forms

EPA Form 3540-8, ***Application for the Registration of Pesticide-producing Establishments*** may be obtained from your EPA Regional Office, or from:

Environmental Protection Agency
Office of Compliance Monitoring (EN-342)
401 M Street, S.W.
Washington, DC 20460.

B. Other Types of Registrations and/or Approvals That May Be Needed from Other Federal or State Agencies

Although you may have obtained a Federal registration for your pesticide product, which allows you to distribute and sell your product in the U.S., there are state regulations that you may have to comply with before you can distribute and/or sell the product within that state.

In addition, there may be other approvals that you must obtain in order to use the product in a specific area. The following listing is intended only to provide general information on some of these requirements, or to provide a point of contact. It should be noted that the listing is not all inclusive, nor is it complete. It is your responsibility to comply with all Federal, state and local regulations.

State Regulation of Federally Registered Pesticides

FIFRA section 24(a) states that "A state may regulate the sale or use of any federally registered pesticide or device in the state, but only if and to the extent the regulation does not permit any sale or use prohibited by this Act."

Even though you have obtained a Federal registration for your pesticide product which allows you to distribute and sell the product within the U.S., the various states in which you may wish to distribute and sell your product may have additional requirements for the regulation of pesticides within the state. The requirements vary from state to state, and may include additional data requirements, additional restrictions on pesticide use within their jurisdiction, and licensing requirements. You should contact each state in which you intend to market your product to determine what additional requirements may affect the sale, distribution, or use of your product.

Whom To Contact for Additional Information

For additional information concerning state registration requirements for your federally registered pesticide product, you should contact the pesticide regulatory authority in the state in which you intend to market your product. A list of these state agencies begins on page 76.

Concurrent Jurisdiction of Federal Agencies

The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have several areas of mutual regulatory responsibility which may require review by one or both agencies. These responsibilities include use of pesticides on food contact surfaces, for paper and paperboard (food uses), on medical devices, as human and animal drugs, and in cane and beet sugar mills.

The following is a brief summary of these areas:

Sanitizers (pesticides used on food contact surfaces). Any pesticide product intended for sanitizing inanimate surfaces must be approved by the FDA pursuant to 21 CFR 178.1010. Ingredients in these products are considered to be Indirect Food Additives. EPA will not register sanitizer products unless the active and inert ingredients have been specifically approved or generally recognized as safe by FDA. Persons who wish to obtain FDA approval must submit a Food Additive Petition or similar request to:

Division of Food and Color Additives (HFF-330)
Food and Drug Administration
200 C Street, S.W.
Washington, DC 20204

Microbiocides in Paper and Paperboard (Food Use). FDA evaluates the safety and efficacy of pesticides used in paper or other materials which come into contact with food. FDA must approve the ingredients of a pesticide as indirect food additives under 21 CFR 176 before EPA will approve a registration. Petitions or requests may be sent to the same address as above.

Human and Animal Drugs. FDA and EPA have areas of mutual responsibility with respect to applications for drugs under FFDCA and for registration of pesticides under FIFRA. In 1971, FDA and EPA issued a Memorandum of Agreement stating which Agency has primary or secondary responsibility on specific matters (See Federal Register Notice, 36 FR 24234). This agreement was updated in 1973 (38 FR 24233) and in 1979 (44 FR 63749). Briefly, EPA has primary jurisdiction for disinfectants and sanitizers, treatments of certain pests on animals, aquatic treatments solely for algae or bacterial slime, sanitizers for aquarium equipment, and sanitizers for inanimate surfaces or drinking water of animals which do not claim disease control. FDA has primary jurisdiction for new human or animal drugs, and for products which are intended to: control parasites on humans, relieve the effect of insect bites, prevent diaper rash through treatment of diapers, treat athletes foot, treat certain animal diseases and pests, treat water for fish parasites or diseases, and treat drinking water to control animal parasites or diseases. Questions on these areas of jurisdiction may be referred to EPA's Antimicrobial Program Branch, Office of Pesticide Programs.

C. Risk/Benefit Assessment

Pesticides are biologically active chemicals that kill or modify the behavior of problem insects, animals, microorganisms, weeds, and other pests. With pesticides, farmers can grow more and greater varieties of food more cheaply; home owners can control pests in their lawns,

gardens, and homes; and public health officials can control pests potentially harmful to our health. But there are disadvantages as well as benefits from using pesticides. By law, EPA must weigh the risks of pesticides to human health and the environment against their benefits with a multi-step process called risk/benefit balancing.

RISK ASSESSMENT. There are four steps in EPA's risk assessment process: hazard identification, dose/response assessment, exposure assessment, and risk characterization.

Hazard Identification. EPA evaluates a pesticide's inherent toxicity - i.e., the types and degrees of harmful effects a pesticide may cause. This is done principally by evaluating laboratory studies conducted on animals. For example, laboratory studies attempt to determine if a chemical is an eye irritant, causes acute poisoning, causes birth defects, or causes cancer, among other effects.

Dose/Response Assessment. A pesticide's potential for causing adverse health effects is identified through a battery of short-term, or acute, and long-term, or chronic, toxicity testing. In several series of tests, laboratory animals are exposed to different doses of a pesticide, and EPA scientists evaluate the tests to find the level of exposure in each of those studies that did not cause any non-cancer effect. This level is called the No-Observed-Effect-Level, or NOEL. The most appropriate NOEL is divided by an uncertainty factor, usually 100 or more, to determine what is called the Reference Dose (RfD) (once known as the Acceptable Daily Intake, ADI). At or below this level, it is assumed that daily exposure over a lifetime will not pose significant risks to health. In addition, EPA routinely requires multi-year laboratory animal feeding studies to screen pesticides for cancer effects. The Agency uses a negligible risk standard to address the risk of cancer from exposure to a pesticide through the food supply. EPA defines a negligible risk to mean that the estimated cancer risk can

be no greater than a risk of 1 in 1 million or less (meaning that, at most, an individual would have a 1 in 1 million chance of developing cancer if exposed over a lifetime).

Exposure Assessment. Once harmful health effects are identified in the laboratory tests, EPA must estimate the level, duration, frequency, and route of exposure for people. For example: Are people who regularly mix and apply pesticides exposed? Is there a chance of exposure to people through food and drinking water? Can plants and animals other than the targeted pests be harmed or killed by the pesticide?

Risk Characterization. Finally, the risk from exposure to pesticides is estimated by integrating the above factors. By combining estimates of likely or actual pesticide exposure with the data on toxicity of the pesticide, EPA can characterize the risks that it poses. This usually involves extrapolating exposure in animals to humans because little direct information about the effects on humans is available. EPA relies on animal studies, assuming that the human response is qualitatively similar to that of animals and that humans will be at least as sensitive, and frequently, more sensitive to the effects of the pesticides.

BENEFIT ASSESSMENT. EPA conducts a benefit assessment when deciding on whether to cancel a pesticide, and evaluates benefits when approving the use of a new pesticide under a conditional registration. The purpose of a benefit assessment is to determine the effectiveness and economic value of a pesticide compared to alternative chemical and non-chemical controls. A benefit assessment is specific for each registered use site (e.g., corn, soybeans, tomatoes, etc.). Essentially, a benefit assessment is an analysis of likely economic consequences resulting from the restriction or cancellation of a pesticide, and includes the following two analyses:

Biological Analysis. The purpose of this analysis is to identify the importance of the pesticide in controlling the intended pest. As part of this process, EPA collects information on the nature and extent of the pest problem, the effectiveness of the pesticide and other chemical and non-chemical controls, and the biological impacts of controlling the pest. For agricultural pesticides, the analysis would compare the effects on crop yield or quality for the pesticide and its alternatives; the information is used to determine the pesticide's value in the production of the crop.

Economic Analysis. An economic analysis translates the biological impact of yield loss, reduced crop quality, and alternative pest control methods into economic terms. EPA evaluates the economic impacts that are expected to occur for all of the affected sectors of the economy. For agricultural pesticides, economic effects include the costs and ability of farmers to produce the crops and, where appropriate, the subsequent costs to consumers who purchase those foods. In addition, secondary effects such as local employment are evaluated when appropriate. A low-cost pesticide that produced substantial benefits to farmers, resulted in lower food costs to consumers, and had few alternatives would be rated as having high benefits. On the other hand, if there were several alternatives to a pesticide that were comparably priced and equally effective, the pesticide would have relatively low benefits.

Tolerances

As a part of its program to regulate the use of pesticides, EPA is responsible for setting tolerances, which are the maximum amount of pesticides that may remain in or on food and animal feed. Tolerances are set at levels to ensure that the public (including infants and children) is

protected from unreasonable health risks posed by eating foods that have been treated with pesticides in accordance with label directions.

To set tolerances that are protective of human health, EPA needs information about the anticipated amount of pesticide residues found on food, the toxic effects of these residues, and estimates of the types and amounts of foods that make up our diet. A tolerance petitioner (generally a pesticide manufacturer) begins the tolerance-setting process by proposing a tolerance level, which is based on field trials reflecting the maximum residue that will occur as a result of the proposed use of the pesticide. The petitioner also must provide food residue and toxicity studies to show that the proposed tolerance would not pose an unreasonable health risk.

Studies of Pesticide Residues in Foods. EPA requires petitioners to submit several types of information to estimate the amount and type of pesticide residues that may remain in food products. One requirement is for product chemistry data, which is information about the content of pesticide products, including the concentration of the ingredients and any impurities. EPA also requires information about how plants and animals metabolize (break down) pesticides to which they are exposed, and whether residues of the metabolized pesticides are detectible in food or feed. Any products of pesticide metabolism, or metabolites, that may be significantly toxic are considered along with the pesticide itself in setting tolerances.

Field experiments are required for pesticides and their metabolites for each crop or crop group for which a tolerance is requested, including each type of raw food derived from the crop. In these studies, the pesticide is applied to crops in a manner similar to that described by the use directions that eventually will appear on the pesticide label if the tolerance petition is approved. Finally, pesticide manufacturers must provide information

on residues found in many processed foods (such as raisins), and in animal products if animals are exposed to pesticides directly or through their feed.

Toxicology Studies. A pesticide's potential for causing adverse health effects - such as cancer, birth defects and other reproductive disorders, and adverse effects on the nervous system or other organs - is identified through a battery of toxicity tests. Tests are conducted for both short-term, or acute, toxicity and long-term, or chronic, toxicity. In several series of tests, laboratory animals are exposed to different doses of a pesticide, and EPA scientists evaluate the tests to find the level of exposure in each of those studies that did not cause any non-cancer effect. This level is called the No-Observed-Effect-Level, or NOEL. When evaluating pesticides for potential effects other than cancer, the Agency divides that level by an uncertainty factor, usually 100 or more, to determine what is called the Reference Dose (RfD). (This 100-fold factor compensates for the fact that humans could be more sensitive than the animals used in laboratory tests.) At or below the RfD, it is assumed that daily exposure over a lifetime will not pose significant risks to health. In addition, EPA routinely requires multi-year laboratory animal feeding studies to screen pesticides for cancer effects.

Food Consumption Estimates. The next step in the process is to estimate the amount of the pesticide to which the public may be exposed through the food supply. EPA uses the Dietary Risk Evaluation System (DRES) to estimate the amount of pesticide in the daily diet, which is based upon a national food consumption survey conducted by the U.S. Department of Agriculture. The USDA survey provides information about the diets of the overall U.S. population and a number of subgroups, including several different ethnic groups, regional populations, and age groups, such as infants and children.

Tolerance Decisions. Finally, for non-cancer risks EPA compares the estimated amount of pesticide in the daily diet to the Reference Dose. If the DRES analysis indicates that the dose consumed in the diet by the general public or key subgroups exceeds the Reference Dose, then generally EPA will not approve the tolerance. Similarly, for potential carcinogens, EPA ordinarily will not approve the tolerance if the dietary analysis indicates that exposure will cause more than a negligible risk of cancer (i.e., the theoretical risk is more than about 1 in 1 million).

EPA believes that the tolerance process is protective of human health because it is based on extensive animal tests and on a combination of conservative assumptions and risk assessment practices. Tolerances are set at the lowest level necessary to accommodate the maximum application rate and frequency being approved for the pesticide use, even if higher levels would be safe for human consumption.

Enforcing Tolerances. Tolerances are enforced by the Food and Drug Administration (FDA), the U.S. Department of Agriculture (USDA), and state enforcement agencies. Before food and feed products enter the channels of trade, inspectors commonly sample food and feed so that any violations may be traced to their sources. Tolerances established by EPA apply equally to domestically grown and to imported food. Imported foods may be denied entry into to the U.S. if they are found to contain pesticide residue levels that exceed the established U.S. tolerances, or for which there are no U.S. tolerances.

Experimental Use Permit

Experimental Use Permits (EUPs) are issued under FIFRA section 5 to allow prospective registrants to generate information or data necessary to register a pesticide under section 3 of FIFRA. You should refer to 40 CFR 172 for detailed information on EUPs. In general, EUPs are issued for:

A pesticide not registered with the EPA, or a registered pesticide for a use not registered with the EPA.

Pesticides under EUPs may not be sold or distributed other than through participants in the approved experimental use program. They may be used only at the application site of a cooperator in the program, and only in accordance with the terms and conditions of the experimental use permit.

When Is an Experimental Use Permit Required?
Generally, an EUP is required before you can conduct large-scale field testing. Large-scale field testing would be any instance other than those described below. However, in certain cases (e.g., novel microbial pesticides certain genetically altered and non-indigenous microbial pest control agents as discussed below), small-scale field tests may require an EUP.

IMPORTANT NOTE: EUPs are required for field testing of pesticides in any indoor situation, for example, a pesticide to control roaches in domestic dwellings, institutions, etc.

EUPs are generally presumed not to be required for a substance or mixture of substances being put through laboratory or greenhouse tests, or limited replicated field trials, in which the purpose is only to determine its value for pesticidal purposes or to determine its toxicity or other properties, under the following circumstances:

1) **Land use** - For tests conducted on a cumulative total of not more than 10 acres involving use of the test material against a particular pest, provided that any food or feed crops involved in or affected by the tests are destroyed or consumed only by experimental animals, unless a tolerance or exemption from a tolerance has been established.

2) **Aquatic use** - For tests conducted on a total of not more than 1 surface-acre of water involving use of a test material against a particular pest, provided that such waters involved in or affected by the tests will not be used for irrigation, drinking water supplies, or body contact recreational activities. In addition, no tests may be conducted in waters that contain, or which affect any fish, shellfish, or other plants or animals which may be taken and used for food or feed unless a tolerance or exemption from a tolerance has been established.

3) **Animal treatments** - For tests conducted only on experimental animals. No animal may be tested if it may be used for food or feed purposes, unless a tolerance or exemption from a tolerance has been established.

Small-scale Field Testing for Novel Microbial Pesticides Requiring an EUP. Due to concerns about the capability of microorganisms to reproduce and multiply in the environment and the potential for these microbials to cause unforeseen adverse impacts, EPA may require an EUP for small-scale field testing of certain novel microbial pesticides (i.e., genetically altered and nonindigenous microbial pest control agents). Refer also to the section on Application Requirements for an Experimental Use Permit, below.

Application Requirements for an Experimental Use Permit. Your application for an EUP must contain or address the following:

GENERAL REQUIREMENTS: Conventional, Biochemical, and Most Microbial Pesticides:

1) "Application for Experimental Use Permit," EPA Form 8570-17.

2) EPA Registration Number of the product to be used, if registered.

3) Purpose or objectives of proposed testing.

4) A detailed description of the proposed testing program including:

   a) Test parameters.

   b) A designation of the pest organism(s) involved.

   c) The amount of pesticide product proposed for use.

   d) The crops, fauna, flora, sites, modes, dosage rates, and situations of application on or in which the pesticide is to be used.

   e) The states, and counties within the state, in which the proposed program will be conducted.

   f) The number of acres, structural sites, or animals, by state and county, to be treated or included in the area of experimental use.

   g) The proposed dates or period(s) during which the testing program is to be conducted.

   h) The manner in which supervision of the program will be accomplished.

5) The name, street address, telephone number, and qualifications of all participants in the program (whether or not in the employ of the applicant). A participant is any person acting as a representative of the permittee and responsible for making available for use, or supervising the use or evaluation of an experimental pesticide to be applied at a specific application site.

6) The name and street address of all cooperators, if available at the time the application is submitted or as soon as possible thereafter. Cooperators are

persons who grant permission for an experimental use pesticide to be used on application sites which they own or control.

7) Information on prior testing - a description and the specific results of any appropriate prior testing of the product conducted by the applicant to determine:

   a) Toxicity and effects in or on any target organisms at the site of application, and

   b) Phytotoxicity and other forms of toxicity or effects on non-target plants, animals, and insects at or near the site of application, or

   c) Any adverse effects on the environment.

8) The proposed method of storage and disposition of any unused experimental pesticide and its containers.

9) Any other additional pertinent information as the EPA may require.

Small-scale Field Testing - Novel Microbial Pesticides (i.e., genetically altered and nonindigenous microbial pest control agents). Prior to the initiation of any small-scale field testing which involves genetically altered or non-indigenous microbial pest control agents, the research organization, company, or individual must submit a notification to the EPA so that a determination can be made as to whether an EUP is required.

Tolerance Requirements. If the proposed experimental use pesticide is to be used in such a manner that any residue can reasonably be expected to result in or on food or feed, the applicant must either:

1) submit evidence that a tolerance or an exemption from the requirement of a tolerance has been established for residues of the pesticide in or on such food or feed under section 408 of the Federal Food Drug and Cosmetic Act (FFDCA), or a regulation promulgated under section 409 of that Act, or

2) submit a request proposing establishment of a tolerance or a temporary tolerance under FFDCA section 408, or a regulation under section 409.

In lieu of submitting a request for a tolerance or temporary tolerance, the applicant may certify that the food or feed item resulting from the experimental use program will be destroyed or fed only to experimental animals for testing purposes.

Data Requirements. If the proposed EUP is for an unregistered pesticide, the following information and/or data are required:

1) Completed Confidential Statement of Formula, EPA Form 8570-4.

2) Appropriate data in accordance with the data requirements identified in 40 CFR 158 for an EUP.

3) Reentry data, if available.

Submitted data (3 copies) must be bound and formatted in accordance with the requirements of PR Notice 86-5.

Labeling Requirements. All pesticides shipped or used under an EUP must be labeled with directions and conditions for use including the following:

1) The prominent statement **"For Experimental Use Only."**

2) The Experimental Use Permit number.

3) The statement **"Not for sale to any person other than a participant or cooperator of the EPA-approved Experimental Use Program."**

4) The name, brand, or trademark.

5) The name and address of the permittee, producer, or registrant.

6) The net contents.

7) An ingredient statement.

8) Warning or caution statements.

9) Any appropriate limitations on entry of persons into treated areas.

10) The establishment registration number, except in those cases where application of the pesticide is made solely by the producer.

11) The directions for trial use.

Extensions or Renewal of Experimental Use Permits. Experimental Use Permits and associated temporary tolerances are usually issued for a period of 1 or 2 years. The permit and any associated temporary tolerances, may be extended, renewed, or amended upon written request to the Agency, if circumstances warrant.

Fee Requirements. If your application for an EUP is accompanied by a petition for a tolerance, temporary tolerance, an exemption from the requirement of a tolerance or a temporary tolerance exemption, the petition is subject to fee requirements. An extension or renewal request for a temporary tolerance is also subject to a fee requirement.

Whom To Contact for Additional Information

Please contact the appropriate Product Manager for your pesticide if you have any questions such as whether an EUP is required, whether a temporary tolerance is required for the proposed use, the appropriate fee, how to submit the application for an EUP, or data required to support the application. If you have questions concerning the testing of novel microbial pesticides, you should contact Product Manager 17 for insecticide products. If you have questions concerning the testing of insecticide, rodenticide, piscicide, or novel microbial pesticides, you should contact Product Manager 18. Product Manager 21 should be contacted for fungicide or herbicide products.

D. Pesticide Reregistration

The Environmental Protection Agency (EPA) is required by law to reregister existing pesticides that originally were registered years ago when standards for government approval were less stringent than they are today. This comprehensive reevaluation of pesticide safety is critical to protecting human health and the environment and maintaining public confidence in our food supply. In 1988, Congress amended the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to strengthen and accelerate EPA's reregistration program. The following is an overview of the 9-year reregistration scheme mandated by FIFRA '88, which applies to each registered product containing any active ingredient registered before November 1, 1984.

List of Pesticides To Be Reregistered

In 1988, approximately 600 groups of related pesticide active ingredients, or cases, representing 1,150 active ingredients in 45,000 formulated products required reevaluation. Following FIFRA '88 requirements, EPA divided these 600 cases into 4 lists: Lists A, B, C, and D.

List A. List A consists of 194 chemical cases (350 individual active ingredients) for which EPA had issued Registration Standards prior to the effective date of FIFRA '88. The Registration Standards program, begun in 1980, was a systematic process for reevaluating existing pesticides. Each Registration Standard summarized available information for a given pesticide case, and identified the conditions that registrants had to meet before EPA would reregister it, such as submitting additional data. In 1988, the 194 Standards issued accounted for about 85 percent of the total volume of conventional pesticides used in the United States.

Lists B, C, and D. The remaining pesticides were divided into three lists based upon their potential exposure and other factors, with List B being of highest concern and D of least. Some of the classification criteria included potential for residues of concern in food or drinking water; significance of outstanding data requirements; potential for worker exposure; Special Review or restricted use status; and unintended adverse effects to animals and plants.

The Reregistration Process

FIFRA '88 established mandatory reregistration time frames and duties. The law requires EPA to complete its reregistration over approximately a 9-year period. The five phases of the reregistration process are described below. Because EPA had already performed substantial review of the List A chemicals under the Registration Standards program, in essence List A chemicals move directly to Phase 5. Products of registrants who fail to comply with the requirements of any of the phases are subject to cancellation or administrative suspension action.

Phase 1: Listing of Active Ingredients. FIFRA '88 required EPA to publish lists A, B, C, and D within 10 months. As required, EPA also asked registrants of these pesticides whether they intended to seek reregistration.

Phase 2: Declaration of Intent and Identification of Studies. Phase 2 required registrants to: notify EPA whether or not they intended to reregister their products; identify and commit to providing necessary new studies; and pay the first installment of the registration fee. During this phase, EPA issued guidance to registrants for preparing their Phase 2 and Phase 3 responses. Phase 2 activities were completed during 1990.

Phase 3: Summarization of Studies. During Phase 3, following EPA guidance, registrants were required to submit summaries and reformatted acceptable studies, flag studies indicating adverse effects, recommit to satisfying all applicable data requirements, and pay the final installment of the registration fee. Phase 3 ended in October 1990.

Phase 4: EPA Review and Data Call-in's. In Phase 4, EPA must review all Phase 2 and 3 submissions and require registrants to meet any unfulfilled data requirements within 4 years. Phase 4 ended in July 1992.

Phase 5: Reregistration Decisions. In this phase, EPA reviews all the studies that have been submitted for a chemical case, and decides whether or not to reregister products containing the active ingredients in that case. A pesticide will be considered eligible for reregistration if its data base is substantially complete, and if it does not cause unreasonable adverse effects to people or the environment when it is used according to product label directions and restrictions.

Status of Reregistration

The overall trend for all four lists is a substantial reduction in the number of pesticides being supported for reregistration by pesticide companies. The number of chemical cases being considered for reregistration declined from about 600 in 1988 to about 400 in early 1991. Pesticide product registrations declined from about 45,000 to 20,000-25,000. Registrants are not supporting reregistration for about half of the original List B, C, and D active ingredients.

EPA generally views this decline in pesticide product registrations as a positive result. In many instances, the pesticides that dropped out had not been produced or marketed for many years. However, the decline in pesticide registrations could have a negative impact on pesticide users who depend on so-called minor uses, specialty pesticide uses with limited market potential. EPA is participating in joint government, industry, and user efforts to help preserve needed minor uses.

EPA issued the first six Reregistration Eligibility Documents (REDs) by early 1991, and expects to issue many more during the next few years. REDs announce that products containing the active ingredient are eligible for reregistration; products will be reregistered once product-specific data and labeling are submitted to and accepted by the Agency. Even after a pesticide is reregistered, however, EPA will continue to reassess it based on new information that becomes available. Reregistration is but one major milestone in a continuing review process.

In conclusion, as a result of FIFRA '88, EPA has greatly accelerated the pesticide reregistration process. A new and more efficient infrastructure has been developed, and EPA is moving ahead briskly with the reregistration effort.

The wave of reregistration decisions will rise steadily during the 1990's, until the task set forth by Congress and the American public is completed.

E. Devices

Section 25(c)(4) of FIFRA provides that the Administrator may specify devices which are subject to any provision of FIFRA section 2(q)(1) or section 7. Devices are defined in FIFRA section 2(h).

The Agency's policy concerning its authority and activities with respect to devices was published in the Federal Register of November 19, 1976 (41 FR 51065).

Definition of Devices

40 CFR 153.240 defines a device as any instrument or contrivance (other than a firearm) which is intended for trapping, destroying, repelling, or mitigating any pest or any other form of plant or animal life (other than man and other than bacterium, virus, or other microorganism on or in living man or other living animals); but not including equipment used for the application of pesticides (such as tamper-resistant bait boxes for rodenticides) when sold separately therefrom.

In general, if an article uses physical or mechanical means to trap, destroy, repel, or mitigate any plant or animal life declared to be a pest at 40 CFR 152.5, it is considered to be a device, and not subject to registration under FIFRA section 3. However, if the article incorporates a substance or mixture of substances intended to prevent, destroy, repel, or mitigate any pest, it is considered to be a pesticide and as such is subject to registration under FIFRA section 3.

Devices Subject To the Act

The Agency, in the November 19, 1976, Federal Register notice, stated that devices subject to FIFRA section 2(q)(1) and section 7 include but are not limited to:

1) Certain ultraviolet light systems, ozone generators, water filters and air filters (except those containing substances which are pesticides), and ultrasonic devices, for which claims are made to kill, inactivate, entrap, or suppress the growth of fungi, bacteria, or viruses in various sites,

2) Certain high-frequency sound generators, carbide cannons, foils, and rotating devices, for which claims are made to repel birds,

3) Black light traps, fly traps, electronic and heat screens, fly ribbons, and fly paper for which claims are made to kill or entrap certain insects, and

4) Mole thumpers, sound repellents, foils and rotating devices, for which claims are made to repel certain mammals.

IMPORTANT NOTE: Although not specifically mentioned in the November 19, 1976, Federal Register notice, the Agency has determined that electromagnetic devices are also subject to FIFRA section 2(q)(1) and section 7.

Devices Not Subject To the Act

The November 19, 1976, Federal Register Notice provided the following examples of those types of devices that are not subject to FIFRA:

1) Devices which depend for their effectiveness more upon the performance of the person using the device than on the performance of the device itself, and

2) Devices which operate to entrap vertebrate animals.

Products generally falling within these two categories include rat and mouse traps, fly swatters, tillage equipment for weed control, and fish traps.

Requirements for Devices

Registration Not Required. A device is not required to be registered under FIFRA section 3. However, devices are subject to certain other requirements of FIFRA as indicated below.

Labeling Requirements. Devices are subject to the labeling requirements of FIFRA section 2(q)(1) and 40 CFR 156. These requirements are summarized below.

a. Under FIFRA section 2(q)(1) a device is considered to be misbranded and subject to enforcement action if:

1) its labeling bears any statements, designs, or graphic representations that are false or misleading (see b. below for examples of false or misleading statements),

2) its packaging or wrapping does not conform to standards established pursuant to FIFRA section 25(c)(3) (as of this date, such standards have yet to be established for devices),

3) it is an imitation of, or is offered for sale under the name of another device,

4) its label fails to bear the establishment number,

5) its label does not display required information prominently,

6) it lacks adequate directions for use, or

7) it lacks an adequate warning or caution statement.

b. 40 CFR 156.10 (a)(5) provides the following examples of labeling statements or representations which constitute misbranding:

1) A false or misleading statement concerning the composition of the product,

2) A false or misleading statement concerning the effectiveness of the product as a pesticide or device,

3) A false or misleading statement about the value of the product for purposes other than as a pesticide or device,

4) A false or misleading comparison with other pesticides or devices,

5) Any statement directly or indirectly implying that the pesticide or device is recommended or endorsed by any agency of the Federal Government,

6) A true statement used in such a way as to give a false or misleading impression to the purchaser,

7) Label disclaimers which negate or detract from labeling statements required under the Act and regulations, and

8) Non-numerical and/or comparative statements on the safety of the product.

Establishment Registration and Reporting, Books and Records. Devices are subject to the establishment registration and reporting requirements found in FIFRA section 7 and 40 CFR 167. All establishments in which devices subject to the Act are produced must be registered with the Agency as producing establishments. This includes foreign establishments in which devices shipped to the U.S. are produced, as well as establishments located in the U.S. which produce devices for export.

FIFRA section 8 and 40 CFR 169 provide information on such records that are required to be maintained by producers of devices.

Inspection of Establishments. Refer to FIFRA section 9 for information concerning inspection of establishments.

Violations, Enforcement Activities, and Penalties. Refer to FIFRA sections 12, 13, and 14 for information concerning violations, enforcement activities, and penalties.

Importation and Exportation of Devices. Refer to FIFRA section 17 for information concerning the importation and exportation requirements for devices. Regulations (19 CFR 12.1) for the implementation of section 17 were published in the Federal Register (40 FR 32321) August 1, 1975. These regulations require, in part, that devices produced by foreign manufacturers and imported into the United States comply with all requirements applicable to domestic producers. In addition, the regulations require an importer to submit to EPA a Notice of Arrival of Pesticides and Devices (EPA Form 3540-1) for review and determination as to whether the shipment should be sampled and/or permitted entry into the United States.

FIFRA section 17 states that no device produced solely for export to any foreign country shall be deemed in violation of FIFRA, when prepared or packaged to the specifications or directions of the foreign producer, except that producers of such devices are subject to sections 2(p), 2(q)(1)(A),(C),(D), (E), (G), and (H), 2(q)(2)(A), (B), (C)(i) and (iii), and (D).

In addition, devices are subject to the record keeping and inspection requirements in accordance with section 8 of FIFRA.

Child-resistant Packaging. Refer to FIFRA section 25(c)(3) and 40 CFR 157.20 for information concerning child-resistant packaging requirements.

Whom To Contact for Additional Information

If you have any questions concerning devices, whether they are subject to the Act, or establishment registration, please contact the Office of Compliance Monitoring, Compliance Division (EN-342), Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Telephone: 202-260-7835.

F. State Regulatory Authority Under FIFRA

State Issuance of Experimental Use Permits

Section 5 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizes any state to issue an EUP for a pesticide in accordance with a state plan approved by the Agency. 40 CFR 172, Subpart B, State Issuance of EUP, provides detailed information on state EUPs. In general, authorized states can issue EUPs for the purpose of gathering data necessary to support the

state registration of a pesticide to meet special local needs under FIFRA section 24(c) and for the purpose of experimentation.

To date, Idaho, Florida, and Vermont have received authorization from the Agency to issue state EUPs.

Whom To Contact for Additional Information

For additional information concerning state EUPs, you should contact the pesticide regulatory authority in the state in which you wish to obtain a state EUP. A listing of the state regulatory agencies can be found on page 76.

State Registration of Special Local Needs

FIFRA section 24(c) authorizes a state to provide registration for additional uses of federally registered pesticides formulated for distribution and use within that state to meet special local needs in accordance with the provisions of the Act. 40 CFR 162, Subpart D - Regulations Pertaining to State Registration of Pesticides to Meet Special Local Needs, provides detailed information on the scope and authority of the states to issue registration of pesticide products.

Under FIFRA section 24(c), states are authorized to register new end-use products or additional uses of federally registered pesticides if there is:

1) a special local need for that product use,

2) the use, if a food or feed use, is covered by an appropriate tolerance or has been exempted from the requirement of a tolerance,

3) registration for the same use has not previously been denied, disapproved, suspended, or canceled by EPA, and

4) the EPA has registered products that contain the active ingredient(s), and each of the inert ingredients is contained in a federally registered product.

Requests for Special Local Need (SLN) registrations are generally made by pesticide companies to the specific state. If the state approves the application, the SLN registration issued by the state is then forwarded to the EPA for acknowledgment.

The EPA has 90 days from receipt of the SLN application from the state to either disapprove or deny the application, otherwise it becomes a Federal registration under FIFRA section 3.

Once the SLN is registered under FIFRA, it is subject to any additional data requirements that may be required by the EPA either as the result of a Registration Standard or any other FIFRA section 3(c)(2)(B) data call-in.

Fee Requirements for SLNs

The 1988 amendments to FIFRA requiring that annual maintenance fees be paid by registrants of pesticide products apply to registrations under section 24(c) of FIFRA.

Emergency Exemptions

FIFRA section 18 authorizes the Administrator to exempt state and Federal agencies from any provision of FIFRA, if he or she determines that emergency conditions exist which require an exemption. The regulations in 40 CFR 166 establish procedures by which the Administrator may exempt a Federal or state agency from the provisions of FIFRA which regulate the manner in which a pesticide is made available for use or is used.

Whom To Contact

Additional information concerning applications for a state SLN registration should be addressed to the state in which you wish to make an application for an SLN registration.

PART II: Environmental Protection Agency

Section 3. Interaction With EPA

How To Obtain Publications

Documents Available From the National Technical Information Service. The listing entitled Availability of OPP Publication Listings includes information on various Office of Pesticide Programs (OPP) documents that are available at the National Technical Information Service (NTIS). The listing includes information on the following:

1) Information for Ordering OPP Publications from the NTIS

2) Registration Standards Report

3) Pesticide Fact Sheets

4) Special Review Position Documents

5) Hazard Evaluation Division (HED) - Pesticide Assessment Guidelines

6) Hazard Evaluation Division (HED) - Standard Evaluation Procedures

7) Pesticide Product Information - Compact Label File

8) Miscellaneous Publications/Documents

9) Pesticide Data Submitters List by Chemical (listed under Miscellaneous Publications/Documents)

Copies of the listing, which includes the NTIS document order number, the EPA document number and the cost of the document on either microfiche or hard copy, are available from:

U.S. EPA
Document Management Section (H7502C)
Information Services Branch, PMSD
Office of Pesticide Programs
401 M Street, S.W.
Washington, DC 20460
Telephone: 703-305-5613

Documents Available From the U.S. Government Printing Office. The following documents are for sale, and are available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

Code of Federal Regulations, Title 40 (40 CFR)

- 40 CFR, Part 2 - Public Information
- 40 CFR, Parts 150 to 189 - Protection of Environment

The Code of Federal Regulations is also available for examination at Government depository libraries and many other libraries. A complete listing of only Government depository libraries is available without charge from The Library, U.S. Government Printing Office, 5236 Eisenhower Avenue, Alexandria, VA 22304. A listing of libraries where the Code of Federal Regulations is available, which includes both Government depository libraries and other libraries that maintain copies of the Code of Federal Regulations can be found in the Federal Register of April 18, 1989 (54 FR 15608).

Documents Available From the Environmental Protection Agency. The following documents are available from the Environmental Protection Agency:

Federal Insecticide, Rodenticide, and Fungicide Act, as amended, October, 1988. EPA 540/09-89-012.

General Information on Applying for Registration of Pesticides in the United States, June, 1989.

Listing of Federally Registered Restricted Use Pesticides. The listing provides, by active ingredient, information on those active ingredients and products that have been classified as Restricted Use pesticides.

Copies of the three documents listed above are available from the following address:

Environmental Protection Agency
Office of Pesticide Programs
Registration Division
Registration Support Branch (H7505C)
401 M Street, S.W.
Washington, DC 20460
Telephone: 703-305-7700

Chemicals for Which Data Waivers Have Been Granted. As outlined in 40 CFR 158.45(d), Agency decisions on data waivers are available to the public at the following location:

Environmental Protection Agency
Office of Pesticide Programs
Docket Reading Room, Room 1128
Crystal Mall #2
1921 Jefferson Davis Highway
Arlington, VA 22202

Office hours are from 8:00 AM to 4:00 PM, EST, Monday through Friday, except legal holidays. Telephone: 703-305-5805

Written Requests: Any person may obtain a copy of any waiver decision by written request to the following address:

Environmental Protection Agency
Freedom of Information (A-101)
401 M Street, SW
Washington, DC 20460

Listing of Registration Standards Issued. This listing, entitled the Registration Standard Report, provides information of all Registration Standards which have been issued, is contained in a general listing entitled OPP Publication Listings (see above).

PR NOTICES. Pesticides Regulation Notices (PR Notices) are mailed to registrants of record when issued. Additional copies, or back copies, are available from:

U.S. EPA
Document Management Section (H7502C)
Information Services Branch, PMSD
Office of Pesticide Programs
401 M Street, S.W.
Washington, DC 20460
Telephone: 703-305-5613

FEDERAL REGISTER NOTICES. The Federal Register is available for examination at Government depository libraries and many other libraries. A complete listing of only Government depository libraries is available without charge from The Library, U.S. Government Printing Office, 5236 Eisenhower Avenue, Alexandria, VA 22304. A listing of libraries where the Federal Register is available, which includes both Government depository libraries and other libraries that maintain copies of the Federal Register, can be found in the Federal Register of April 18, 1989 (54 FR 15608).

Forms, and How To Obtain Them.

The various forms required to be submitted with various types of applications for registration, EUPs, and distributors are listed below.

EPA FORM	TITLE
8570-1	Application for Pesticide Registration/Amendment (Revised 9-88, previous editions are obsolete)
8570-4	Confidential statement of Formula (Revised 2-85, previous editions are obsolete)
8570-5	Notice of Supplemental Registration of Distributor (Revised 4-83, previous editions are obsolete)
8570-6	Certification of Attempt to Enter Into an Agreement with Other Registrants for Development of Data (10-82)
8570-17	Application for an Experimental Use Permit to Ship and Use a Pesticide for Experimental Purposes Only (Revised 2-85, Previous editions may be used until supply is exhausted)
8570-20	Data Reference Sheet (1-81)
8570-27	Formulator's Exemption statement (10-86)

8570-28	Certification of Compliance with Data Gap Procedures (10-86)
8570-29	Certification with Respect to Citation of Data (7-86)

Copies of these forms may be obtained from the Registration Support Branch, Registration Division (H5704C), Office of Pesticide Programs, Washington, DC 20460. Telephone: 703-305-7700.

The following forms may be obtained from the Office of Compliance Monitoring (EN-342), 401 M Street, SW, Washington DC, 20460, or your EPA regional office.

EPA FORM	TITLE
3540-1	Notice of Arrival of Pesticides or Devices
3540-8	Application for Registration of Pesticide-Producing Establishments

Contact for Assistance and Where To Send Your Applications and Submissions

General Information. The Registration Division, Office of Pesticide Programs, consists of three pesticide product branches, the Insecticide-Rodenticide Branch, the Fungicide-Herbicide Branch, the Antimicrobial Program Branch, and one support branch, the Registration Support Branch. The pesticide product branches are further subdivided into Product Manager Teams which are responsible for the review and processing of applications for registration, amended registration, petitions for tolerances, and EUPs.

Where To Submit Your Application

1) Applications for registration, petitions, EUPs, etc., must be mailed to the following address:

Document Processing Desk
Office of Pesticide Programs (H7504C)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

** Insert Appropriate Distribution Code identified below.

2) Hand-delivered applications must be delivered to the following address:

U.S. Environmental Protection Agency
Crystal Mall, Bldg. #2, Room 258
Document Processing Desk (H7504C)
1921 Jefferson Davis Highway
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AMEND	Application to Amend a Product Registration
BIOTECH	Biotech Applications and pre-EUP Notifications
DIST	Supplemental (Distributor) Registration
EUP	Application for an Experimental Use Permit
PETN	Petition Request for Tolerance/Exemption
SLN	Special Local Need Registration
CAN/WD	Request to Cancel a Registered Product or to Withdraw a Pending Application for Registration, Experimental Use Permit, Petition, etc.
NEWCO	Request for a Company Number (Register an Establishment)
COADR	Company Name and Address Change
XFER	Transfer Products to a Different Company

EPA Regional Offices

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Environmental Protection Agency
John F. Kennedy Federal Building, Room 2203
Boston, MA 02203
617-565-3424

REGION 2 — Jurisdiction: New Jersey, New York, Puerto Rico, Virgin Islands

Environmental Protection Agency
26 Federal Plaza
New York, NY 10278
212-264-2515

REGION 3 — Jurisdiction: Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, West Virginia

Environmental Protection Agency
841 Chestnut Street
Philadelphia, PA 19107
215-597-9370

REGION 4 — Jurisdiction: Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee

Environmental Protection Agency
345 Courtland Street, N.E.
Atlanta, GA 30365
404-347-3004

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Environmental Protection Agency
230 South Dearborn Street 5 SPT 7
Chicago, IL 60604
312-353-2072

REGION 6 Jurisdiction: Arkansas, Louisiana, New Mexico, Oklahoma, Texas

Environmental Protection Agency
1445 Ross Avenue 12th Floor, Suite 1200
Dallas, TX 75202
214-655-2200

REGION 7 Jurisdiction: Iowa, Kansas, Missouri, Nebraska

Environmental Protection Agency
726 Minnesota Avenue
Kansas City, KS 66101
913-551-7003

REGION 8 Jurisdiction: Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming

Environmental Protection Agency
One Denver Place
999 18th Street, Suite 1300
Denver, CO 80202
303-293-1692

REGION 9 — Jurisdiction: Arizona, California, Hawaii, Nevada, American Samoa, Guam, Trust Territory of the Pacific

Environmental Protection Agency
75 Hawthorne Street
San Francisco, CA 94105
415-744-1305

REGION 10 — Jurisdiction: Alaska, Idaho, Oregon, Washington

Environmental Protection Agency
1200 Sixth Avenue
Seattle, WA 98101
206-553-1107

State Agencies With Lead Pesticide Responsibility

Alabama

Director
Ag Chemistry/Plant Industry Division
Alabama Dept. of Agriculture & Industry
P.O. Box 3336
Montgomery, AL 36193
205-261-2631

Alaska

Pesticide Specialist
Alaska Dept. of Environmental Conservation
500 S. Alaska St., Suite A
Palmer, AK 99645
907-745-3236

American Samoa	Director American Samoa EPA Office of the Governor Pago Pago, American Samoa 96799
Arizona	State Chemist Office of State Chemist P.O. Box 1586 Mesa, AZ 85211-1586 602-833-5442
Arkansas	Director Div. of Feed, Fertilizer & Pesticides Arkansas State Plant Board P.O. Box 1069 Little Rock, AR 72203 501-225-1598
California	Chief Pesticide Registration Branch Division of Pest Management California Dept. of Food & Agriculture 1220 N Street, Room A-447 Sacramento, CA 95814 916-322-5130
Colorado	Chief Pesticide Applicator Section Division of Plant Industry Colorado Dept. of Agriculture 4th Floor, 1525 Sherman Street Denver, CO 80203 303-866-2838

Commonwealth of the Northern Mariana Islands	Chief Division of Environmental Quality Commonwealth of the Northern Mariana Islands (CNMI) P.O. Box 1304 Saipan, MP 96950
Connecticut	Senior Environmental Analyst Pesticide Control Section Department of Environmental Protection State Office Building Hartford, CT 06106 203-566-5148
Delaware	Pesticide Compliance Supervisor Delaware Dept. of Agriculture 2320 South DuPont Highway Dover, DE 19901 302-736-4811
District of Columbia	Section Chief Pesticide Section Environmental Control Division Dept. of Consumer & Regulatory Affairs 5010 Overlook Avenue, S.W. Room 114 Washington, DC 20023 202-727-7432

Florida	Administrator Pesticide Registration Section Bureau of Product Data Evaluation Division of Inspection Florida Dept. of Agric. & Consumer Services Mayo Building, Room 208A Tallahassee, FL 32399-0800 904-487-2130
Georgia	Ag. Manager II Entomology & Pesticide Division Georgia Department of Agriculture Capitol Square Atlanta, GA 30334 404-656-4958
Guam	Director Air & Land Programs Division Guam Environmental Protection on Agency Harmon Plaza Complex, Unit D-107 130 Rojas St. Harmon, GU 96911
Hawaii	Registration Specialist Pesticides Branch Plant Industry Division Hawaii Department of Agriculture 1428 South King Street Honolulu, HI 96814 808-548-7125

Idaho	Supervisor Pesticide Programs Division of Plant Industries Idaho Dept. of Agriculture P.O. Box 790 Boise, ID 83701-0790 208-334-3243
Illinois	Chief Bureau of Plant & Apiary Protection Illinois Dept. of Agriculture State Fairgrounds Springfield, IL 62791-9281 217-785-2427
Indiana	Pesticide Compliance Officer Indiana State Chemist Office Dept. of Biochemistry Purdue University West Lafayette, IN 47907 317-494-1585
Iowa	Supervisor Pesticide Section Iowa Dept. of Agriculture Wallace Bldg. East 7th Street and Court Avenue Des Moines, IA 50319 515-281-8591
Kansas	Administrator Pesticide Registration Plant Health-Division Kansas Dept. of Agriculture 109 S.W. Ninth Street Topeka, KS 66612-1281 913-296-2263

Kentucky	Director Kentucky Dept. of Agriculture Capitol Plaza Tower Frankfort, KY 40601 502-564-7274
Louisiana	Director Pesticides & Environmental Programs Louisiana Dept. of Agriculture P.O. Box 44153 Baton Rouge, LA 70804-4153 504-925-3763
Maine	Pesticides Registrar Board of Pesticides Control Maine Dept. of Agriculture State House Station #28 Augusta, ME 04333 207-289-2731
Maryland	Registrar State Chemist Section Plant Industries & Resource Conservation Maryland Dept. of Agriculture 0233 Chemistry Bldg. College Park, MD 20742 301-454-2722
Massachusetts	Manager Technical Assessment Section Pesticides Bureau Massachusetts Dept. of Food and Agriculture 100 Cambridge Street, 21st Floor Boston, MA 02202 617-727-7712 or 2863

Michigan	Supervisor Product Registration Pesticide & Plant Management Division Michigan Dept. of Agriculture P.O. Box 30017 Lansing MI 48909 517-373-1087
Minnesota	Pesticide Control Specialist, Agronomy Services Division Minnesota Dept. of Agriculture 90 West Plato Blvd. St. Paul, MN 55107 612-297-2530
Mississippi	Pesticide Registration Division of Plant Industry Dept. of Agriculture and Commerce P.O. Box 5207 Mississippi State, MS 39762 601-325-3390
Missouri	Supervisor Bureau of Pesticide Control Plant Industries Division Missouri Dept. of Agriculture P.O. Box 630 Jefferson City, MO 65102-0630 314-751-2462

Montana

Chief
Technical Services Bureau
Environmental Management Division
Montana Dept. of Agriculture
Agriculture-Livestock Bldg.
Capitol Station
Helena, MT 59620-0205
406-444-2944

Nebraska

Director
Bureau of Plant Industry
Nebraska Dept. of Agriculture
301 Centennial Mall
Lincoln, NE 68509
402-471-2341

Nevada

Director
Division of Plant Industry
Nevada Dept. of Agriculture
P.O. Box 11100
Reno, NV 89510-1100
702-789-0180

New Hampshire

Director
Division of Pesticide Control
New Hampshire Dept. of Agriculture
Caller Box 2042
Concord, NH 03301
603-271-3550

New Jersey

Chief
Bureau of Pesticide Control
New Jersey Dept. of Environmental Protection
401 East State Street CN 411
Trenton, NJ 08265
609-530-4134

New Mexico	Chief Bureau of Pesticide Management Division of Agric. & Environmental Sciences New Mexico Dept. of Agriculture P.O. Box 30005, Dept. 3AQ Las Cruces, NM 88003 505-646-2133
New York	Director Bureau of Pesticide Management Dept. of Environmental Conservation Room 404, 50 Wolf Road Albany, NY 12233-7254 518-457-7482
North Carolina	Assist. Pesticide Administrator Food & Drug Protection Division North Carolina Dept. of Agriculture P.O. Box 27647 Raleigh, NC 27611-0647 919-733-3556
North Dakota	Director Registration Division North Dakota Dept. of Health & Consolidated Labs P.O. Box 937 Bismarck, ND 58502 701-221-6149

Ohio	Specialist in Charge Pesticides Regulation Ohio Dept. of Agriculture Division of Plant Industry 8995 East Main Street Reynoldsburg, OH 43068-3399 614-866-6361
Oklahoma	Program Manager Pesticide Registration Program Oklahoma Dept. of Agriculture 2800 North Lincoln Blvd. Oklahoma City, OK 73105-4298 405-521-3864
Oregon	Program Coordinator Plant Division Oregon Dept. of Agriculture 635 Capitol Street, N.E. Salem, OR 97301 503-378-3776
Pennsylvania	Use & Investigation Specialist Bureau of Plant Industry Division of Agronomic Services Pennsylvania Dept. of Agriculture 2301 N. Cameron Street Harrisburg, PA 17110 717-787-4843

Puerto Rico	Director Analysis & Registration of Agricultural Materials Puerto Rico Dept. of Agriculture P.O. Box 10163 Santurce, PR 00908 809-796-1710, 1735
Republic of Palau	Executive Officer Palau Environmental Quality Protection Board Republic of Palau P.O. Box 100 Koror, Palau 96940
Rhode Island	Senior Plant Pathologist Division of Agriculture & Marketing Dept. of Environmental Management 22 Hayes Street Providence, RI 02908 401-277-2782
South Carolina	Department Head Dept. of Fertilizer & Pesticide Control 256 Poole Agricultural Center Clemson, SC 29634-0394 803-656-3171

South Dakota	Supervisor, Pesticide Activity Division of Regulatory Services South Dakota Dept. of Agriculture Anderson Bldg. 445 East Capitol Pierre, SD 57501 605-773-3724
Tennessee	Pesticide Registration Division of Plant Industries Tennessee Dept. of Agriculture P.O. Box 40627 Melrose Station Nashville, TN 37204 615-360-0130
Texas	Director Texas Dept. of Agriculture P.O. Box 12847 Austin, TX 78711 512-463-7526
Utah	Director Division of Plant Industry Utah Dept. of Agriculture 350 North Redwood Road Salt Lake City, UT 84116 801-533-4107
Vermont	Director Plant Industry Laboratory & Standards Division Vermont Dept. of Agriculture 116 State Street State Office Bldg. Montpelier, VT 05602 802-828-2435

Virginia	Supervisor Office of Pesticide Regulation Virginia Dept. of Agriculture & Consumer Service P.O. Box 1163 Richmond, VA 23209 804-786-3798
Virgin Islands	Director Pesticide Programs Division of Natural Resources Management Dept. of Conservation and Cultural Affairs P.O. Box 4340 St. Thomas, VI 00801 809-774-6420
Washington	Chief Registrations & Services Washington Dept. of Agriculture 406 General Administration Bldg. AX-41 Olympia, WA 98504 206-735-5064
West Virginia	Administrator Regulatory & Inspection Division W. Virginia Dept. of Agriculture Charleston WV 25305 304-348-2208

Wisconsin	Certification & Licensing Wisconsin Dept. of Agriculture, Trade, Consumer Protection P.O. Box 8911 Madison, WI 53708 608-267-9148
Wyoming	Manager Technical Services Wyoming Dept. of Agriculture 2219 Carey Avenue Cheyenne, WY 82002-0100 307-777-6590

PART III

ANIMAL AND PLANT HEALTH INSPECTION SERVICE

Section 1. Legal Authority

A. Virus-Serum-Toxin Act

The Virus-Serum-Toxin (VST) Act and regulations published in 9 CFR 101-118 provide the U.S. Department of Agriculture (USDA) the authority to regulate all veterinary biological products shipped into, within, or from the United States. The regulations in 9 CFR 101.2(w) define veterinary biological products to be "all viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals."

The VST Act makes it unlawful to (sell) worthless, contaminated, dangerous, or harmful veterinary biologics, or to ship veterinary biologics in or from the United States unless they are prepared in a licensed establishment in compliance with USDA regulations. An exemption from this licensing provision is given for products prepared by (1) a person solely for administration in that person's own animals, (2) a veterinarian for use in her or his own licensed practice under a veterinarian-client-patient

relationship, and (3) a person operating a state-licensed facility solely for distribution of product within the state of production. However, the state must have a state regulatory control program for veterinary biologics that has been reviewed by USDA and found to be acceptable. The Act also gives USDA the authority to make and issue regulations to prevent the preparation and marketing of worthless, contaminated, dangerous, or harmful veterinary biologics and to inspect manufacturing facilities, manufacturing processes, and the veterinary biological product itself. It requires the issuance of a permit by USDA prior to importation of veterinary biological products and gives the Department the authority to test imported products prior to distribution if desired.

The VST Act also provides for the issuance of conditional or special licenses for products on the basis of purity, safety, and a reasonable expectation of efficacy in order to meet an emergency condition, limited markets or local situation, or other special circumstance.

In case of violation, the Act permits USDA to remove or suspend establishment and/or product licenses provided the licensee is given the opportunity for a hearing prior to such action. It also gives authority for detention, seizure, and condemnation of products and injunction against products or establishments. Criminal action that could lead to a fine or imprisonment may also be taken against violators.

B. Organizational Structure

Within USDA, the authority for administering the VST Act has been delegated to the Animal and Plant Health Inspection Service (APHIS). Four of the ten units within APHIS, each with specific responsibilities, must coordinate their activities for program delivery. These units are:

1) Veterinary Biologics (VB), a staff located in Hyattsville, Maryland, is responsible for the development of licensing and permit requirements; review of license and permit applications; development and publication of program policy and procedures in regulations, standard requirements, memorandums, notices; program planning and budgeting; and coordination of informal hearings concerning violations that could lead to suspension or revocation of licenses.

2) Veterinary Biologics Field Operations (VBFO), a line unit located in Ames, Iowa, has responsibility for inspection of manufacturing facilities and processes, release of products for marketing, monitoring the use of products after release, and coordination of investigations to assure compliance with the VST Act and regulations.

3) National Veterinary Services Laboratories (NVSL), also in Ames, Iowa, supports the VB and VBFO through extensive product testing prior to licensing, development of new test methods, preparation of test references and reagents, and check testing of products after licensing to assure the purity, safety, and potency of veterinary biologics. Through its advisory role to the other units, the NVSL provides a strong scientific base for the program.

4) Regulatory Enforcement and Animal Care, a staff and field unit within APHIS, is responsible for supporting the VBFO through investigation of alleged violations of the Act and regulations.

Section 2. Biological Products

A. Licensing Procedures

In order to produce and market a veterinary biological product in the United States, a producer needs two kinds of licenses, as described in 9 CFR 102:

1) A U.S. Veterinary Biologics Establishment License for each production facility and

2) A U.S. Veterinary Biological Product License for each product produced in a licensed establishment.

Procedures for the issuance of establishment and product licenses in the United States are designed to define and document what is being licensed and who will be responsible for the production and distribution of the product that is being authorized. They are also intended to assure the purity, safety, potency, and efficacy of each product and the accuracy of labeling.

A staff reviewer is assigned to work with each license applicant and to guide the applicant through the licensing process. Staff officers also review protocols of proposed research to be conducted to support product license applications to assure the study design is valid, statistically sound, and acceptable for the purpose intended.

B. Veterinary Biologics Establishment License

To obtain a U.S. Veterinary Biologics Establishment License, an application (APHIS Form 2001) must be filed with APHIS that identifies the name and address of the applicant and any subsidiaries or divisions that will be

doing business under the license. The application also identifies the responsible person for the license including corporate officers for corporations. The application must be supported by:

1) an application for a U.S. Veterinary Biological Product License,

2) a copy of the articles of incorporation if the applicant or subsidiaries are incorporated,

3) plot plans and blueprints of the facilities to be licensed and a legend that provides a brief description of the activities performed in each room including decontamination procedures and other precautions against cross contamination,

4) a certificate from the appropriate water pollution control agency that the establishment is in compliance with applicable water control standards, and

5) a short resume of training and experience of those employees at the establishment who will be responsible for essential steps in production, testing, and initial distribution of product.

Prior to the issuance of a license for the establishment, VBFO personnel will conduct a prelicensing inspection of the facilities. Inspectors will review the adequacy of recordkeeping systems, construction and operation of the establishment, quality control procedures, and laboratory practices. A person at the establishment will be trained to collect and submit valid samples from each serial of product for testing at NVSL. Compliance requirements will also be reviewed at this time. The report of the prelicensing inspection is forwarded to VB for consideration in the licensing process. If found satisfactory in all regards, the establishment license will be issued with the first product license.

C. Veterinary Biological Product License

A U.S. Veterinary Biological Product License is required for each product produced in a licensed establishment. An Application for a U.S. Veterinary Biological Product License (APHIS Form 2003) must be filed for each product in accordance with 9 CFR 102.5. If an establishment is not already licensed, an application for an establishment license must accompany the application for a product license. Product license applications must be supported by: (1) an outline of production, (2) legend changes, (3) sketches and/or final labels, and (4) supporting data.

The outline of production is the detailed protocol for manufacturing and testing the product and should be prepared and submitted in accordance with 9 CFR 114.8 and 114.9. The outline includes information such as:

For each microorganism-the source and date of accession, the isolation and passage history, strains and proportion of each;

Cultures-the method of identification of each microorganism, virulence and purity data, all media composition, seed culture storage, inoculation technique;

Harvesting-handling of cultures and media, time from inoculation to harvest, technique for harvesting microorganisms;

Product preparation-stepwise description from harvest of antigen to the finished product in final containers;

Testing-stages at which samples are collected, reference to applicable Standard Requirements defined in 9 CFR, details of additional tests giving minimum requirements for each satisfactory test;

Other information-final container sampling, calculation of expiration date, recommendations for use, dosage, and route of administration.

Data must be provided to support the purity, safety, potency, and efficacy of product produced in accordance with the outline of production. The use of a Master Seed as the source of all seed production assists in maintaining uniformity of production. In most cases, final product must not be more than five serial passages from the Master Seed.

All product ingredients must meet accepted standards of purity and quality. Master cell stock, Master Seed, ingredients of animal origin not subjected to heat sterilization, and final product must be tested and shown to be free of extraneous bacteria, fungi, mycoplasma, and viruses.

Product immunogenicity must be demonstrated by statistically valid host animal vaccination and challenge studies. The vaccination must be conducted using minimum levels of antigen with product produced at the highest passage level from the Master Seed that is permitted for production. The precise challenge method and the criteria for determining protection vary with the immunizing agent. For example, duration of immunity data requires challenge 1 or 3 years postvaccination for rabies vaccines.

A minimum of 20 vaccinates and 5 controls are generally required for immunogenicity testing. In most cases, 19 of 20 vaccinates must be shown to be protected against a challenge that kills 4 of 5 controls, with the fifth control demonstrating severe signs of the disease. In the case where 95 percent efficacy cannot be expected for the product or the challenge organism is not pathogenic enough to cause death, other parameters, such as the scoring of clinical signs or pathology, are used in the evaluation of the test.

Field efficacy studies have been accepted in the licensing of products when a meaningful laboratory challenge model cannot be established. Field efficacy studies must include valid controls and an adequate number of animals to demonstrate a significant effect from the use of the product. It is more difficult to obtain valid efficacy data under field studies than in the laboratory. In some cases a combination of laboratory and field efficacy studies may be needed to assure efficacy.

The efficacy of each label indication must be established. That is, each route or method of administration, each species of animal for which the product is recommended, and any claims for degree of protection afforded must be supported prior to approval.

Potency tests are designed to correlate with the host animal vaccination and challenge studies. Prior to release, each serial, i.e., production lot, is tested for potency. For killed viral or bacterial products, potency tests may be conducted in laboratory or host animals or with quantitative in vitro methods. For release of live vaccines, bacterial counts or virus titrations are used. The bacterial count of a live bacterial vaccine for release must be sufficiently greater than that used in the immunogenicity test to assure that when tested at any time within the expiration period the titer will be at least twice that used in the immunogenicity test. For release of virus products, the titer must be adequate to assure that when tested at any time within the expiration period the titer will be at least five times that used in the immunogenicity test.

Stability studies (based on an acceptable potency test) are required to establish the validity of the expiration date given on the product package. For preliminary stability studies, the product may be incubated at 37°C for a short time (e.g., a week), but these results should be confirmed by potency tests through the period of time indicated by the expiration date, and 6 months beyond.

Safety testing can be a combination of various studies. Mouse intracranial, subcutaneous, or intraperitoneal tests are acceptable for the final product. For anaerobes, the guinea pig appears to be very sensitive for evaluating safety. Host animal safety data are also required.

Environmental safety is an important issue for live viral or live bacterial vaccines, and in particular for live recombinant products. Live products must be characterized to determine if they have the ability to shed from the host and transmit to contact animals. Back passage studies are required to provide information on genetic stability and on what can be expected when that vaccine is put into animals in the field. Once laboratory characterization studies are completed, field tests provide additional safety data.

All veterinary biological products for use in animals must be tested for safety in the field before licensure. Field safety studies are designed to detect unexpected reactions, including mortality, that may not have been observed during the development of the product. The firm must meet the requirements indicated in 9 CFR 103.3 for shipping experimental products; this includes obtaining permission from the proper animal health authorities for each state where the tests will take place.

The tests are done on the host animal, at a variety of geographical locations, using large numbers of susceptible animals that the firm does not own. The test animals should represent all the ages and husbandry practices for which the product is indicated. The product tested should be one or more of the three prelicense serials. A detailed protocol for the field safety study must be submitted to VB for review. The protocol should indicate the observation methods and the recording methods.

Scientists from the NVSL or inspectors from VBFO may be requested by VB to observe any of the firm's pre-licensing laboratory or field studies. For those studies not observed by APHIS personnel, records may be reviewed during inspections.

Licensees are required to produce and test three consecutive satisfactory serials of final product in their licensed establishment in accordance with the approved Outline of Production. Samples of these serials are forwarded to NVSL for prelicense testing to confirm the producer's test result.

After completing the tests on samples of the three consecutive prelicense serials (all applicable Standard Requirement and special tests in the Outline of Production), the firm sends the results to VB for review. If the test results are satisfactory, VB sends a computer message to the NVSL requesting the NVSL to confirm the firm's tests on samples of the three prelicense serials. Confirmation testing of selected product serials continues after licensure. Selection of samples is established by the procedures given in 9 CFR 113.3.

Upon satisfactory completion of all requirements, including review and acceptance of labels and circulars, a U.S. Veterinary Biological Product License may be issued.

The Outline of Production, plot plans, blueprints, and legends that are developed and filed during the licensing process must be complied with and represent a contract of how the product must be produced. These documents and the regulations serve as the basis for the release of individual serials and for in-depth inspections conducted by VBFO personnel at licensed establishments after licensing.

D. Alternate Licensing Procedures

Through experience, APHIS has found the use of conditional licenses, licenses for further manufacture, and sublicensing procedures to be very beneficial.

In order to meet an emergency condition, limited market or local situation, or other special circumstance, APHIS may issue a conditional (special) license under an expedited procedure on such conditions as are considered necessary to assure the purity, safety, and a reasonable expectation of efficacy. In addition to an expedited procedure to meet emergency disease outbreaks, conditional licensure provides a mechanism for the licensing of products for minor species and other limited market situations where the cost of establishing full efficacy before marketing would prohibit the development of needed products. This type of license has also been issued when host animal efficacy has been established but difficulty in the development of a fully satisfactory potency test would result in undue delay in the issuance of a regular license. Conditional licenses are issued for a period of 1 year. Before reissuance, the licensee must demonstrate acceptable progress toward completion of host animal efficacy and/or potency tests in accordance with protocols filed with APHIS. Labels for conditionally licensed products must bear a statement that the product is under conditional license and that potency and efficacy studies are in progress. Conditional licenses are not issued for any product already issued a regular license.

Licensing products for further manufacture has permitted split manufacturing procedures where two or more establishments can work together to produce a product. These are regular licenses for partially finished products that are only permitted to be shipped from one licensed establishment to another licensed establishment or for export. The receiving company finishes the product and releases it under a regular product license. Licensing in this manner has permitted the industry to take the best

advantage of its production capability and to expand company product lines without extensive developmental costs.

Sublicensing of a licensed product from one company to another is also permitted. In this process, the company that has a license for the product contracts to transfer to the second company the data, technology, and materials necessary to produce the product. The outline of production must be transferred along with Master Seed and any Master Cell stock. The receiving company must repeat purity testing of Master Seed and Master Cell stock and do an immunogenicity test in a reduced number of host animals to confirm previous data. Additional field safety studies are not required. This process has been useful in the transfer of products and technology from one company to another.

E. State and Federal Interaction

As currently written, the VST Act does not have preemptive authority over state laws concerning the regulation of veterinary biological products. Veterinary biological products cannot be shipped in or from the U.S. unless they meet Federal standards; however, states may impose additional requirements if they desire. The Biologics Program, therefore, requires an active interaction with state authorities. Usually, this interaction involves requesting state approval for the distribution of products such as requiring firms to obtain state approval before the authorization of field trials with experimental products or before marketing a conditional licensed product in the state. Some regular licensed products also have restrictions on the license that require firms to obtain approval from the states before distribution of their products.

Section 3. Enforcement

A. Inspections

In-depth inspections of veterinary biologics production companies licensed by the USDA are conducted every 12 to 20 months by teams of veterinarians and/or microbiologists. Inspections are unannounced and may take 2 weeks to complete. The objective of the in-depth inspection is to visit each licensed location and, in the shortest possible time, determine if the company is preparing, testing, and distributing veterinary biologics in compliance with the VST Act, the regulations, and the outline of production.

Each in-depth inspection is made up of three different activities; pre-inspection activities, the inspection proper, and post-inspection activities.

Most of the pre-inspection activities involve reviewing all of the manufacturer's files since the previous inspection. These files consist of:

1) Outlines of Production and Labels for each product approved by VB,

2) Facility Documents approved by VBFO,

3) Testing information provided by the NVSL, and

4) Submissions from the company on unusual situations.

The most valuable source of information is the summary record of production and testing submitted by each company for each serial prepared. Information from these production and testing records is placed in a computer

data base and is used for preparing marketing reports and reviews of firm activity, as well as the inspectors when preparing for an inspection.

For the larger companies where it will not be possible to review everything during the inspection, product records to audit and operations to observe are selected at random. An attempt is made to select these in advance based on information in APHIS' files. High volume products are selected to determine consistency of the manufacturing process and low-volume products are selected to determine if manufacturing expertise is being maintained at a high level.

The in-depth inspection has been organized into 14 categories of inspection. The categories are a listing of numerous audit or observation items to consider when making an inspection. The inspector has the freedom to choose all or none of the items, provided the ultimate objective of the inspection is accomplished. Again, the inspector's main objective is to determine if the company is manufacturing, testing, and distributing veterinary biologics using good laboratory techniques and good sanitary measures in compliance with Federal regulations and according to the Outline of Production. The Outline of Production, approved by VB, is considered to have the force of Federal regulations.

The categories of inspection which the inspector may consider include:

Licenses. The company must still exist and locations used to prepare, test, and distribute veterinary biologics must be inspected and approved. Product licenses may be terminated due to inactivity so it must be determined if products are still in active production. A check is also made to see that the company has followed the restrictions listed on permits to import biological material from other countries.

Personnel. Inspectors check to be sure all personnel changes have been reported.

Facilities. During the in-depth inspection, the information on the drawings and in the legends is reviewed for accuracy and acceptability.

Equipment. Records must be kept on the use and validation of all equipment. Inspectors verify that validation of equipment is occurring and is appropriate for the equipment. As standards change, equipment or the validation systems must be upgraded to meet the new standards.

Sanitation. Each company must submit written procedures for cleaning and disinfecting production areas. During the inspection, procedures being used are verified as appropriate for the biologic being prepared.

Research. The company often has one or more products they have submitted for licensing. The inspector compares the data submitted against the research notebooks, bench records or field trial information to assure that the summary data is accurate. An in-depth review of the research records of one or more products that have already been licensed may be conducted.

Seeds and Cells. The company must provide records that permit tracing from each batch back to the Master Seed. All steps must be documented, including the disposition of all material prepared from the seed. Inspectors check the seed identity and purity testing and confirm that the seed currently used for production is the same seed that was used for the efficacy studies and field trials.

Production. Identification and accountability are the two key issues inspectors look for when inspecting the production process. As many actual procedures as possible are observed during the visit. Other issues to determine are:

Is the product being prepared according to the Outline of Production?

Are records being made accurately and concurrently with the steps in production?

When procedures are not available for observation, inspectors audit the records of the batches that were identified during the pre-inspection process. All material entering the production process and all equipment must be identified. Inspectors trace material back to acquisition and testing and equipment back to the sterilization and validation. The company must account for the disposition of all material and by-products resulting from the production procedures.

Final Production. Filling, lyophilization, controlled freezing, preparation of final containers, and labeling are the focus of this category. As in the previous category, the inspector observes procedures and audits records to determine compliance with the outline and good production procedures.

Labels. Here, the inspector looks for accountability and whether the labels are properly secured and determines if the company is using the exact copy of the label approved by staff.

Testing. In this category, the inspector is encouraged to observe as many activities as possible to determine if the product is being tested according to the standard in the CFR and the Outline of Production. In lieu of observations, predetermined records are audited. The inspector will check to see that the company is using good laboratory practices, proper controls are in place for each test, and all tests are being accurately reported to VBFO.

Animals. Inspectors check to see that animals are being handled using appropriate care and that animals used in production and testing are healthy and have proper veterinary care.

Distribution. Accountability is the key issue in this category. The company must have a system to recall the product if necessary. The Inspector may conduct a mock recall to see whether the company can account for every container that leaves the facility.

Miscellaneous. This category deals with issues not addressed in the other 13 categories.

Samples submitted to the NVSL may be selected only by company employees who have been trained and authorized by an APHIS inspector. The inspector provides training during the inspection. Inspectors also review the company's files on user-reported problems. They look for unusual or unexpected events that have been seen in the field as the result of use of the product. Inspectors must supervise the disposal of all products found to be unsatisfactory by the NVSL.

When infractions of the CFR, the Outline of Production, or good production practices are found, the inspector must decide what action should be taken. All infractions are judged against the VST Act. Inspectors must decide whether the infraction would cause the product to be worthless, dangerous, contaminated, or harmful. Inspectors are authorized to make this decision and take remedial action on the spot.

Inspectors are authorized to make agreements directly with the company to correct deficiencies or infractions. These agreements are usually made at the end of the inspection in a final meeting with company management. Serious infractions involving stopping the distribution and

sale of a product, recall of a product, or temporary suspension of a product license require approval from the Deputy Director, VBFO.

Upon return to the office, the inspection team prepares a summary of its findings. Regulatory actions taken at the company are reviewed by a Senior Inspector and then by the Deputy Director to assure uniformity and consistency with previous actions. Changes can be made at this point. Any new actions are reported to the company before a written report is prepared.

Finally, a written narrative inspection report is prepared. The report documents the general activities of the inspection team, the inspection findings, and the specific infractions found and actions taken.

The team leader will decide when a followup inspection is required to assure that all agreements have been met by the company and compliance has been achieved.

B. Check Testing and Controlling the Release of Serials

Samples of every batch (serial) of product produced in the United States or offered for importation are selected by authorized samplers at the firm or import quarantine facility. The samples are sent to the NVSL for check testing. The NVSL maintains the biologics program data base, which contains information on all licensed products. Serials are tested on a random basis to assure that a high quality level is maintained. The data base contains the testing profiles on some 2,000 licensed products. Approximately 10 percent of the serials submitted are selected for testing. Problem products are tested at a higher rate. Check testing at NVSL is not primarily to certify release of individual serials but is a check on the testing and quality control of the manufacturer.

To reduce delays in releasing satisfactory serials for marketing, APHIS has agreed to initiate testing concurrently with the manufacturer. Upon receipt by NVSL, each serial is vulnerable for testing for 14 days. APHIS has agreed that after 14 days, the serial will no longer be at risk for testing without additional justification, such as reports of field problems, inspection, or investigation findings. The manufacturer is notified if the serial is to be tested after the 14-day period.

The manufacturer must test each serial according to the Outline of Production. Serials may not be marketed before VBFO has had the opportunity to review the results of those tests and the NVSL has had the opportunity to test the serial.

The VBFO receives summaries of test results for every serial of veterinary biologic produced in the United States or offered for importation. The test report form also includes the number and size of final containers and the total number of doses to be marketed.

Upon receipt of the company's production and testing report, an initial review is conducted by a technician using the Outline of Production as a guide. If the information submitted meets the criteria for an acceptable serial, it is entered into the computer data base. If the serial does not appear to be acceptable or there appear to be other problems, the report is given to an inspector for review.

Final review of all reports is conducted by an inspector who certifies that the serial is acceptable for marketing. At this point, check testing conducted by the NVSL is used to confirm the company's test results. Copies of the NVSL's test results are provided to the company for information.

When the final decision is made, the company is notified by telephone that the batch is approved or denied for release. A copy of the report, with the inspector's signature, is returned to the company for record keeping.

C. Monitoring the Use of Veterinary Biologics

The VBFO has established a product monitoring section headed by a board-certified veterinary epidemiologist. The program deals with user complaints from the field and actively identifies and investigates the use of products in the field.

A monitoring review board made up of personnel from all three units reviews the information and investigation results and makes recommendations for changes in inspection, testing, and licensing policy. They also develop and approve surveillance activities to monitor product use. When products are identified that are suspected of not meeting the requirements of the VST Act or the regulations, they are subjected to additional review and testing for possible removal from the market. The group may also recommend changes in the labeling such as additional warnings or changes in use of the product.

The monitoring group also provides the public with additional information about the veterinary biologics program. A 24-hour consumer information hot line has been established to receive information from product users.

D. Investigation Review and Regulatory Action

The VBFO reviews the results of investigations conducted by investigators from Regulatory Enforcement and Animal Care. The VBFO also may conduct investigations of alleged violations in licensed facilities. Based on the investigation findings, recommendations for action are made to the Deputy Director, VBFO.

The Deputy Director, VBFO, is authorized to take some specific regulatory action based on established program policy. All other recommendations are submitted to the Director, Biologics, Biotechnology, and Environmental Production, for final review and action.

PART III: ANIMAL AND PLANT HEALTH INSPECTION SERVICE

Section 4. Interaction With The USDA

A. Licensing and Program Policy Information

For information about obtaining licenses for veterinary biologics or for general program information, contact:

Deputy Director
Veterinary Biologics
USDA, APHIS, BBEP
Room 838 Federal Building
6505 Belcrest Road
Hyattsville, MD 20782
Telephone: 301-436-8245
FAX: 301-436-5992

B. Inspection and Enforcement Information

For general information about inspection or enforcement activities, or to report a violation, contact:

Deputy Director
Veterinary Biologics, Field Operations
USDA, APHIS, BBEP
223 S. Walnut Ave.
Ames, IA 50010
Telephone: 515-232-5785
FAX: 515-232-7120

C. Consumer Information HOT LINE

To report a problem with a veterinary biologic or diagnostic, or for more information about biologics, you may contact the following number:

CONSUMER HOT LINE NUMBER 515-232-5789 (ANSWERED 24-HOURS)

During working hours (Mon-Fri, 7:30 a.m.-5:00 p.m. Central Time) you may call collect. At other times your message will be recorded and one of our inspectors will return your call the next working day.

Veterinary Biologics Contacts Licensing Staff

Dr. David Espeseth
Deputy Director of Veterinary Biologics
Room 838, Federal Building
6505 Belcrest Road
Hyattsville, MD 20782
301-436-8245

Dr. Albert Morgan
Chief Staff Veterinarian, Diagnostic Section
Room 838, Federal Building
6505 Belcrest Road
Hyattsville, MD 20782
301-436-7760

Dr. Cyril Gay
Chief Staff Veterinarian, Biotechnology Section
Room 838, Federal Building
6505 Belcrest Road
Hyattsville, MD 20782
301-436-8674

Dr. Robert Miller
Chief Staff Veterinarian, Virology Section
Room 838, Federal Building
6505 Belcrest Road
Hyattsville, MD 20782
301-436-5863

Dr. Sarah Anne Goodman
Chief Staff Veterinarian, Bacteriology Section
Room 838, Federal Building
6505 Belcrest Road
Hyattsville, MD 20782
301-436-5863

Dr. James Tanner
Chief Staff Biometrician, Biometrics Section
Room 500, Federal Building
6505 Belcrest Road
Hyattsville, MD 20782
310-436-8400

Field Office

Dr. Donald Randall
Deputy Director
Veterinary Biologics Field Operations
233 S. Walnut Avenue
Ames, IA 50010
515-232-5785

Veterinary Biologics Hot Line 515-232-5789

Dr. Tom Bunn
Chief, Bacteriology Lab
USDA, APHIS, VS, NVSL
1800 Dayton Road
Ames, IA 50010
515-239-8266

Dr. Stan Harris
Chief, Virology Lab
USDA, APHIS, VS, NVSL
1800 Dayton Road
Ames, IA 50010
515-239-8266

Glossary

Active Ingredient (pesticide): In any pesticide product, the component which kills, or otherwise controls, target pests. Pesticides are regulated primarily on the basis of their active ingredients.

Acute Toxicity: The capacity of a substance to cause a poisonous effect (such as skin or eye irritation or damage to an organ) or death as a result of a single or short-term exposure.

Adulteration: A violation of the Federal Food, Drug, and Cosmetic Act which includes products that are defective, unsafe, not shown to be safe, filthy, or produced under insanitary conditions. It also includes products which are manufactured under procedures and controls which do not comply with Current Good Manufacturing Practice regulations as well as new animal drug products which are not the subject of an NADA approval. Detailed definitions of adulteration are in the Act itself, and have been developed in regulations and by the courts.

Adverse Drug Reaction: An unexpected side effect, injury, toxicity, sensitivity reaction, or unexpected incidence or severity of side effects associated with use of a new animal drug product. The failure of a new animal drug product to exhibit expected pharmacological action also is an adverse drug reaction.

Animal Feed: An article which is intended for use as a substantial source of nutrients in the diet of the animal. It is not limited to a mixture intended to be the sole ration of the animal.

Biologicals: see **Veterinary Biologicals**

Cancellation: The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) section 6(b) authorizes cancellation of registration if, when used according to widespread and commonly recognized practice, the pesticide generally causes unreasonable adverse effects on the environment, or if its labeling or other material required to be submitted does not comply with FIFRA provisions.

Chronic Toxicity: The capacity of a substance to cause harmful health effects after long-term exposure.

Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component part or accessory, which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes.

Drug: An article (1) recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; (2) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (3) intended to affect the structure or any function of the body of man or other animals; and (4) intended for use as a component of any articles specified in clause (1), (2), or (3); but does not include devices or their components, parts, or accessories.

Endangered Species: Animals, birds, fish, plants, or other living organisms threatened with extinction by man-made or natural changes in their environment. Requirements for declaring a species are contained in the Endangered Species Act.

Experimental Use Permit: Pesticide manufacturers are required to obtain experimental use permits for testing new uses of pesticides whenever they conduct experimental field studies to support registration of the pesticide on 10 acres or more of land or one acre or more of water.

Extra-Label Use: Refers to the actual or intended use of an approved new animal drug in a manner that is not in accordance with the approved label directions.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA): The statute under which EPA regulates the marketing and use of pesticides in the United States.

FIFRA Section 18: A provision in FIFRA under which EPA can grant an emergency exemption to a state or another federal agency that allows the use for a limited period (usually one year) of a pesticide product that is not registered for that particular use. The exemption is requested and authorized because a pest problem is unanticipated and/or severe and there is no time or interest by a registrant to register the product for that use. Registrants cannot apply for emergency exemptions.

FIFRA Section 24(c): Registration of a pesticide product by a state agency for a specific use that is not federally registered (however, the active ingredient must be federally registered for other uses). The special use is specific to that state and is often minor; thus, it may not economically warrant a full federal registration by the registrant.

Injunction: A writ granted by a court whereby one is required to do or refrain from doing a specific act. In most instances FDA seeks injunctions against individuals and/or corporations to prevent them from violating or causing violations of the Federal Food, Drug, and Cosmetic Act.

Inert Ingredient: A component of a pesticide such as a solvent or carrier that is not active against target pests.

Interregional Research Project No. 4 (IR-4): A program sponsored by the U.S. Department of Agriculture (USDA). IR-4 provides national leadership and coordination for information on the clearance of minor use pesticides and generates data to support minor use registrations.

Investigational New Animal Drug (INAD): Statutory authority to exempt new animal drugs from the requirements of an approved new animal drug application is found in Section 512 (j) of the Federal Food, Drug, and Cosmetic Act. This exemption specifically limits the distribution of unapproved new animal drugs only for use by experts, qualified by scientific training and experience, to investigate the safety and effectiveness of animal drugs. In order to distribute a new animal drug for clinical investigations, an exemption from the requirements of an approved new animal drug application must be claimed. This is accomplished by the submission of certain information referred to as an INAD (Investigational New Animal Drug) application.

Labeling: All labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers or (2) accompanying such article.

Medicated Animal Feed: An article intended for use as food for animals, other than man, bearing, containing, or purporting to bear or contain any kind of animal drug/drug combination.

Medicated Feed Application (Form FDA-1900): A new animal drug application providing for the use of new animal drugs in feed and submitted by the sponsor, manufacturer, or authorized agent.

Microbial Pesticide: A microorganism that is used to control a pest. Microorganisms are living organisms so small that individually they usually can be seen only through a microscope.

Misbranding: A violation of the Federal Food, Drug, and Cosmetic Act which includes among other things statements, designs, or pictures in labeling that are false or misleading, and failure to provide required information in labeling. A detailed definition of misbranding is in the Act and has been developed further in regulations and judicial decisions.

National Pesticide Telecommunications Network (NPTN): Located at Texas Tech University, NPTN is a network from which the public can obtain answers to their pesticide-related questions by calling a toll-free phone number (1-800-858-7378) that is funded by EPA.

National Technical Information Service (NTIS): An organization that sells certain government publications, including EPA documents such as testing guidelines for pesticides. Orders can be placed at NTIS, Attention: Order Desk, 5285 Port Royal Road, Springfield, VA 22161. Telephone number: 703-487-4650.

New Animal Drug: Any drug intended for use for animals other than man which, among other things, is not generally recognized by qualified experts as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof.

Pest: An insect, rodent, nematode, fungus, weed, or other form of terrestrial or aquatic plant or animal life or virus, bacteria, or microorganism considered to be an annoyance and which may be injurious to health or the environment.

Pesticide: Substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. Also, any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant.

Pesticide Assessment Guidelines (PAG): Protocols listed in 40 CFR 158 that provide registrants with guidelines on how to conduct studies. They are published by EPA but are not legal documents. Copies of the PAG can be obtained from the National Technical Information Service.

Pesticide Registration (PR) Notice: A written notice from OPP to pesticide registrants that communicates important changes in regulatory policy, procedures, and or regulations. Each PR Notice is assigned a two-part number beginning with the year issued followed by a cardinal number (e.g., 87-1, 87-2).

Reentry Interval: The period of time immediately following the application of a pesticide to an area during which unprotected workers should not enter the area.

Registrant: Any manufacturer or formulator who obtains registration for a pesticide active ingredient or product.

Registration: Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, as amended), the formal listing with EPA of a new pesticidal active ingredient prior to its marketing or distribution in intra- or inter-state commerce.

Registration Standards: Published documents which include summary reviews of all the data available on a pesticide active ingredient, data gaps identified, and the Agency's existing regulatory position on the pesticide.

Reregistration: The reevaluation and relicensing of existing pesticidal active ingredients originally registered prior to current scientific and regulatory standards.

Phase 1: EPA publishes list of pesticides.

Phase 2: Registrants decide to support chemicals by agreeing to conduct the required studies any by paying maintenance fees.

Phase 3: Registrants summarize and reformat existing studies and certify access to raw data. The registrants flag potential adverse effects data and pay an additional fee to keep chemicals registered.

Phase 4: EPA reviews Phase 2 and 3 submissions and identifies additional data needs. EPA publishes lists of missing studies and notifies registrants of required studies.

Phase 5: All chemical studies must be submitted before this phase. Product-specific studies are required. Once these studies are reviewed and deemed acceptable, products will be reregistered.

Residues (pesticide): The pesticide remaining after natural or technological processes have taken place.

Restricted Use: When a pesticide is registered, some or all of its uses may be classified under FIFRA for restricted use if the pesticide requires special handling because of its toxicity. Restricted-use pesticides (RUP) may be applied only by trained, certified applicators or those under their direct supervision.

Seizure: An action brought under admiralty proceedings against an animal feed, drug, or device which is in violation of the Federal Food, Drug, and Cosmetic Act for being adulterated and/or misbranded. The purpose is to remove a specific lot of goods from the channels of commerce.

Suspension: EPA's act of prohibiting the use of a pesticide in order to prevent an imminent hazard resulting from continued use of the pesticide. An emergency suspension takes effect immediately; under an ordinary suspension, a registrant can request a hearing before the suspension goes into effect.

Tolerance (pesticide): The maximum amount of pesticide residue allowed by law to remain in or on a harvested crop. EPA sets these levels so that the chemicals do not pose an unreasonable risk to consumers. Under the Federal Food, Drug, and Cosmetic Act, EPA is responsible for establishing tolerances. Whenever a pesticide is registered for use on a food or feed crop, a tolerance or exemption from the tolerance must be established. Established tolerances and exemptions for pesticide chemicals in or on raw agricultural commodities are listed in 40 CFR 180. Tolerances for pesticides in processed food are listed at 40 CFR 185; and tolerances for pesticides in processed animal feed are listed at 40 CFR 186. Tolerances are enforced by the Food and Drug Administration and the U.S. Department of Agriculture.

Tolerance Petition (pesticide): A formal request to establish a new tolerance or modify (raise, lower or revoke) existing tolerances.

Toxic: Harmful to living organisms.

Toxicity: The inherent capability of a substance to cause adverse effects in human, animal, or plant life.

Unreasonable Risk (pesticide): Under FIFRA, "unreasonable adverse effects on the environment" means any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide.

Veterinary Biologicals: Viruses, serums, toxins, and analogous products of natural or synthetic origin, such as diagnostics, antitoxins, vaccines, live microorganisms, killed microorganisms, and the antigenic or immunizing components of microorganisms intended for use in the diagnosis, treatment, or prevention of diseases of animals.